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VOLUME 12 OCTOBER 1953 NUMBER 4

ORIGINAL ARTICLES

MAXIMUM BREATHING CAPACITY AND VITAL CAPACITY IN FEMALE CHILDREN AND ADOLESCENTS

By B. G. FERRIS, JR., M.D., AND C. W. SMITH, M.D.*
Boston

ATTEMPTS to evaluate the degree of pulmonary dysfunction in children and adolescents have been greatly handicapped by lack of adequate standards for reference. Adult standards are obviously not applicable to children. The need has been in part fulfilled for male children and adolescents in regard to the maximum breathing capacity and vital capacity. These values do not apply to females. The present study was undertaken to obtain a similar set of standards for female children and adolescents.

METHODS

Female students attending 3 private schools in the vicinity of Boston were used as subjects. A total of 233 girls was studied: at the Beaver Country Day School, which included the Chestnut Hill School, 167 pupils whose ages varied from 5 1/12 to 18 2/12 yr.; at the Park School 29 pupils whose ages varied from 7 1/12 to 17 5/12 yr.; and at the Meadowbrook School 37 pupils varying in age from 5 3/12 to 11 9/12 yr. The subjects were healthy active girls of the Caucasian race.

Vital capacities and maximum breathing capacities were measured in a Benedict-Roth type spirometer (Collins Ventilometer) with the soda lime container and valves removed. The vital capacity used has been defined as a maximal expiration following a maximal inspiration. The largest of 3 or more such measurements was used. The younger children were encouraged to "blow out all the candles on your birthday cake." The indication for more than 3 measurements was a progressive rise in the values obtained. Similarly, the greatest of 3 determinations of the maximum breathing capacity was used; if there was a progressive increase, further determinations were made. Since the training factor in the maximum breathing capacity was considerable, more than 3 runs were often necessary. Intervals of 1 to 2 min. were allowed between these determinations for rest, because when done properly, the maximum breathing capacity is strenuous exercise. These determinations were done by encouraging the subject to breathe as deeply and as rapidly as possible, but allowing her to select

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her own combination of depth and rate. After a few breaths to permit her to reach her maximal effort a 15 sec. period was measured. The values so obtained were extrapolated to 1 min. periods. All measurements were done with the subject standing and free movement of the arms and shoulders was allowed.

The resistance developed in the spirometer system has been reported in a previous study.[1]

All ventilatory values were corrected to conditions of body temperature, ambient pressure and saturation with water vapor at 37°C. (BTPS).* The maximum breathing capacity was recorded to the nearest l./min. and the vital capacity to the nearest 0.01 l.

Subjects were weighed on a platform-type balance scale to the nearest 0.1 kg. without heavy clothing (shoes and coats), and their heights in stocking feet were recorded to the nearest 0.5 cm. Body surface area was obtained from a Dubois nomogram. This was read to the nearest 0.01 M^2. Birth dates were recorded and the age at the time of the ventilatory measurements was calculated to the nearest month. All measurements were made by the same observer.

Results and Discussion

The results are presented in tables 1 to 8 where the average vital capacities and maximum breathing capacities for the various groupings are shown. The individual results have been plotted as scattergrams (charts 1 to 8) against the different physical characteristics (age, height, weight, and body surface area). Smoothed curves for the mean values (solid line) and the two standard deviation ranges (dashed lines) above and below the means have been constructed and plotted on the scattergrams. This means that 95% of normal observations should fall within these two standard deviation limits. If observations are less than the mean minus two standard deviations, there is a 1:40 chance that they are abnormal. Since one is usually concerned whether the values are low rather than high, observations greater than the mean plus two standard deviations are not considered clinically significant.

Contrary to the observations in adolescent males, there is no change in the slope of the curves at the time of the adolescent growth spurt. This may imply that the muscular development associated with this growth spurt is less in girls than in males. Schlesinger[2] has demonstrated that males developed a greater increase in manual pressure associated with puberty than females. Schlesinger stated that this increase in manual pressure did not parallel the increase in the vital capacity. A change in the respiratory muscles similar to that in the hands might explain the difference between the maximum breathing capacity of males and females. A marked increase in the vital capacity of males associated with adolescent growth was observed by Stewart.[3] Such was not the case with his observations in females.

The question can be raised whether this group was a representative sample of female children and adolescents. The students at three schools were used and there was a considerable overlap of the ages in the three schools. The number of observations at the various ages were well distributed. Table 9 presents the average heights and weights and the standard deviations for height and weight for each year of age. When these averages are plotted on the percentile charts of Stuart and Meredith,[4] the average heights follow

$$\text{* Volume corrected}_{\text{BTPS}} = \text{volume observed} \times \frac{310^\circ}{\text{Observed temp. °C.} + 273^\circ} \times \frac{\text{Observed bar. pressure} - \text{Vapor tension of water at observed temperature}}{\text{Observed bar. pressure} - 47 \text{ (Vapor tension of water at 37°C.)}}$$

TABLE 1

VITAL CAPACITY IN L. IN RELATION TO AGE IN YEARS FOR FEMALE CHILDREN AND ADOLESCENTS

Age, yr.	5.0–5.9	6.0–6.9	7.0–7.9	8.0–8.9	9.0–9.9	10.0–10.9	11.0–11.9	12.0–12.9	13.0–13.9	14.0–14.9	15.0–15.9	16.0–16.9	17.0–17.9	18.0–18.9
No.	12	8	18	19	29	22	28	28	14	19	12	10	12	2
Mean, L.	1.08	1.45	1.51	1.87	2.04	2.29	2.57	3.03	3.49	3.40	3.66	3.63	4.00	3.00
Std. Dev., L.	0.17	0.19	0.16	0.32	0.33	0.24	0.43	0.43	0.68	0.49	0.39	0.36	0.42	

TABLE 2

MAXIMUM BREATHING CAPACITY IN L./MINUTE IN RELATION TO AGE IN YEARS FOR FEMALE CHILDREN AND ADOLESCENTS

Age, yr.	5.0–5.9	6.0–6.9	7.0–7.9	8.0–8.9	9.0–9.9	10.0–10.9	11.0–11.9	12.0–12.9	13.0–13.9	14.0–14.9	15.0–15.9	16.0–16.9	17.0–17.9	18.0–18.9
No.	12	8	18	19	29	22	28	28	14	19	12	10	12	2
Mean, LPM	41.2	52.6	52.8	60.3	67.0	71.9	79.3	95.8	103.9	99.4	105	92.0	108.3	123.1
Std. Dev., LPM	10.9	5.2	10.1	12.1	10.5	11.2	14.9	24.3	18.7	30.2	23.2	18.2	24.6	20.1

TABLE 3

VITAL CAPACITY IN L. IN RELATION TO WEIGHT IN KG. FOR FEMALE CHILDREN AND ADOLESCENTS

Wt., kg.	15.0–19.9	20.0–24.9	25.0–29.9	30.0–34.9	35.0–39.9	40.0–44.9	45.0–49.9	50.0–54.9	55.0–59.9	60.0–64.9	65.0–69.9	70.0–74.9	75.0–79.9
No.	6	26	17	29	28	28	24	25	26	15	4	3	1
Mean, L.	1.04	1.40	1.75	1.98	2.37	2.63	3.02	3.24	3.53	3.65	3.55	4.13	3.90
Std. Dev., L.	0.22	0.25	0.26	0.32	0.37	0.48	0.42	0.51	0.58	0.36	0.99	0.36	

TABLE 4

MAXIMUM BREATHING CAPACITY IN L./MINUTE IN RELATION TO WEIGHT IN KG. FOR FEMALE CHILDREN AND ADOLESCENTS

Wt., kg.	15.0–19.9	20.0–24.9	25.0–29.9	30.0–34.9	35.0–39.9	40.0–44.9	45.0–49.9	50.0–54.9	55.0–59.9	60.0–64.9	65.0–69.9	70.0–74.9	75.0–79.9
No.	6	26	17	29	28	28	24	25	26	15	4	3	1
Mean, LPM	36.0	53.0	60.7	65.0	77.6	77.3	87.6	97.6	100.0	105.9	97.9	126.3	131.7
Std. Dev., LPM	5.8	10.0	10.0	13.5	13.4	17.2	19.7	28.9	27.7	23.3	23.6	17.5	

TABLE 5

VITAL CAPACITY IN L. IN RELATION TO BODY SURFACE AREA IN METERS² FOR FEMALE CHILDREN AND ADOLESCENTS

B.S.A., M²	0.60–0.79	0.80–0.89	0.90–0.99	1.00–1.09	1.10–1.19	1.20–1.29	1.30–1.39	1.40–1.49	1.50–1.59	1.60–1.69	1.70–1.79	1.80–1.89
No.	9	18	14	25	30	22	22	24	32	24	9	3
Mean, L.	1.12	1.38	1.64	1.84	2.21	2.39	2.76	3.08	3.29	3.69	4.00	4.20
Std. Dev., L.	0.20	0.26	0.29	0.26	0.28	0.30	0.37	0.54	0.46	0.37	0.42	0.24

TABLE 6

MAXIMUM BREATHING CAPACITY IN L./MINUTE IN RELATION TO BODY SURFACE AREA IN METERS² FOR FEMALE CHILDREN AND ADOLESCENTS

B.S.A., M²	0.60–0.79	0.80–0.89	0.90–0.99	1.00–1.09	1.10–1.19	1.20–1.29	1.30–1.39	1.40–1.49	1.50–1.59	1.60–1.69	1.70–1.79	1.80–1.89
No.	9	18	14	25	30	22	22	24	32	24	9	3
Mean, LPM	41.9	53.0	59.6	63.3	69.8	75.7	81.2	90.8	93.0	106.6	120.6	130.2
Std. Dev., LPM	10.4	11.3	17.7	12.4	11.8	13.1	18.9	22.0	25.1	26.5	17.7	17.1

TABLE 7

VITAL CAPACITY IN L. IN RELATION TO HEIGHT IN CM. FOR FEMALE CHILDREN AND ADOLESCENTS

Ht., cm.	100.0–104.9	105.0–109.9	110.0–114.9	115.0–119.9	120.0–124.9	125.0–129.9	130.0–134.9	135.0–139.9	140.0–144.9	145.0–149.9	150.0–154.9	155.0–159.9	160.0–164.9	165.0–169.9	170.0–174.9
No.	2	2	7	13	10	15	19	30	19	12	23	38	18	17	6
Mean, L.	0.95	1.00	1.12	1.37	1.70	1.70	1.97	2.19	2.32	2.53	2.94	3.28	3.57	3.85	3.91
Std. Dev., L.	0.25	0.10	0.17	0.19	0.35	0.22	0.33	0.27	0.32	0.33	0.30	0.43	0.41	0.44	0.26

TABLE 8

MAXIMUM BREATHING CAPACITY IN L./MINUTE IN RELATION TO HEIGHT IN CM. FOR FEMALE CHILDREN AND ADOLESCENTS

Ht., cm.	100.0–109.9	110.0–114.9	115.0–119.9	120.0–124.9	125.0–129.9	130.0–134.9	135.0–139.9	140.0–144.9	145.0–149.9	150.0–154.9	155.0–159.9	160.0–164.9	165.0–169.9	170.0–174.9
No.	4	7	13	10	15	19	30	19	12	23	38	18	17	6
Mean, LPM	41.5	45.2	49.0	61.7	57.9	62.1	72.0	73.7	77.9	89.8	94.7	102.7	107.3	124.3
Std. Dev., LPM	13.6	8.6	11.0	16.3	9.8	10.6	11.3	13.2	18.4	20.9	21.8	26.4	28.4	14.6

VITAL CAPACITY VS. AGE
IN FEMALE CHILDREN AND ADOLESCENTS

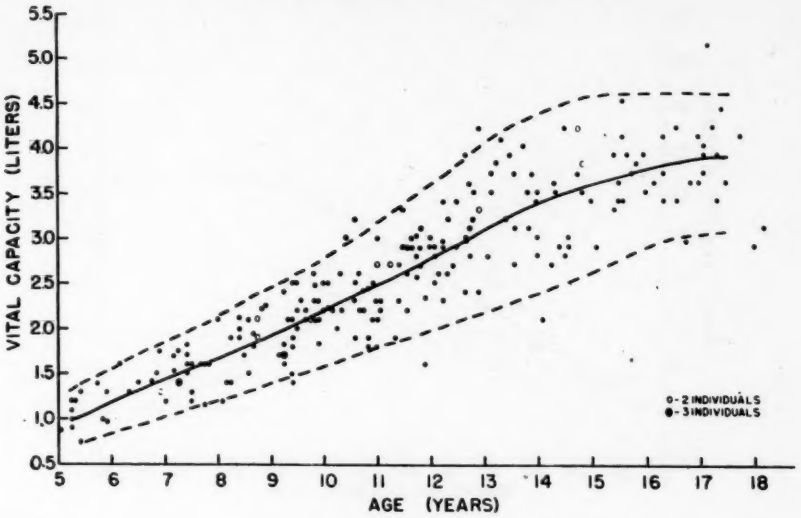
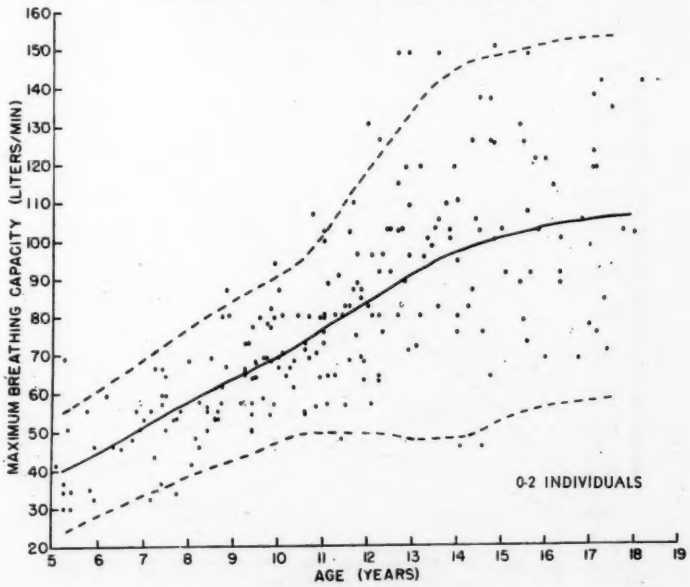


CHART 1

MAXIMUM BREATHING CAPACITY VS AGE
IN FEMALE CHILDREN AND ADOLESCENTS



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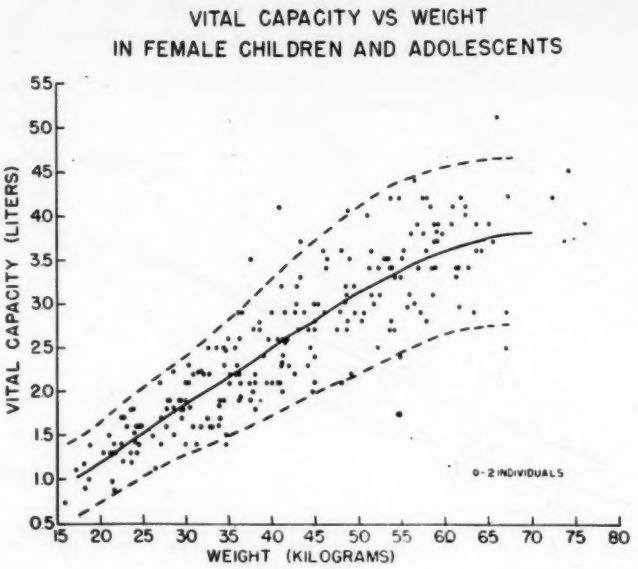

CHART 3

CHART 4

VITAL CAPACITY VS. BODY SURFACE AREA
IN FEMALE CHILDREN AND ADOLESCENTS

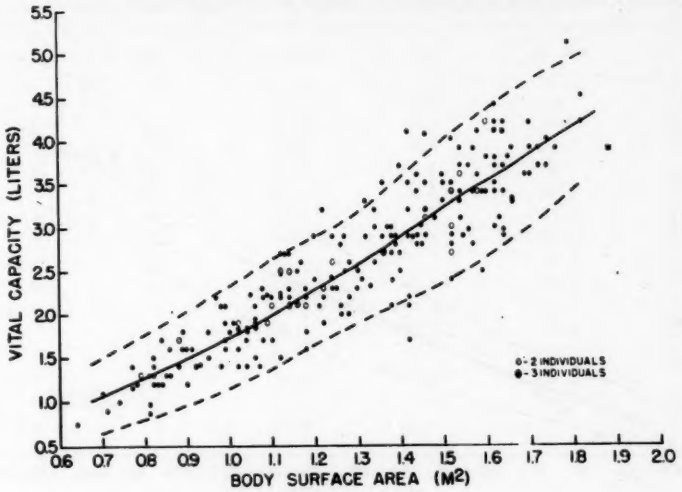

CHART 5

MAXIMUM BREATHING CAPACITY VS. BODY SURFACE AREA
IN FEMALE CHILDREN AND ADOLESCENTS

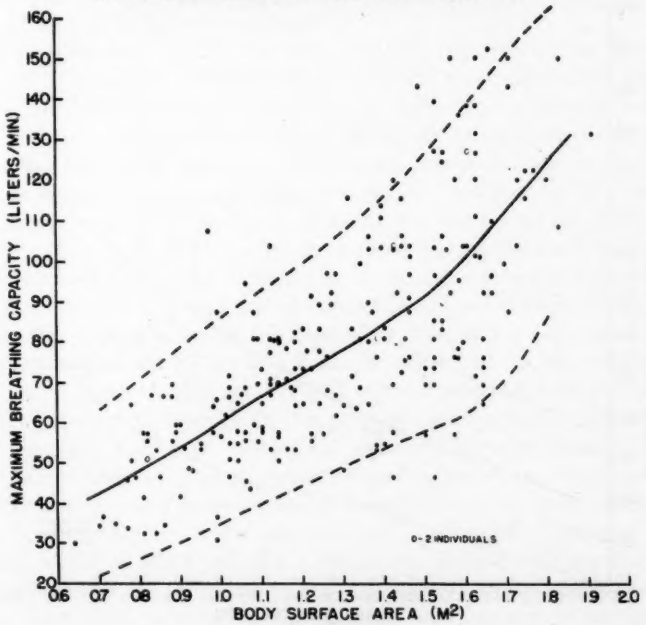

CHART 6

VITAL CAPACITY VS. HEIGHT
IN FEMALE CHILDREN AND ADOLESCENTS

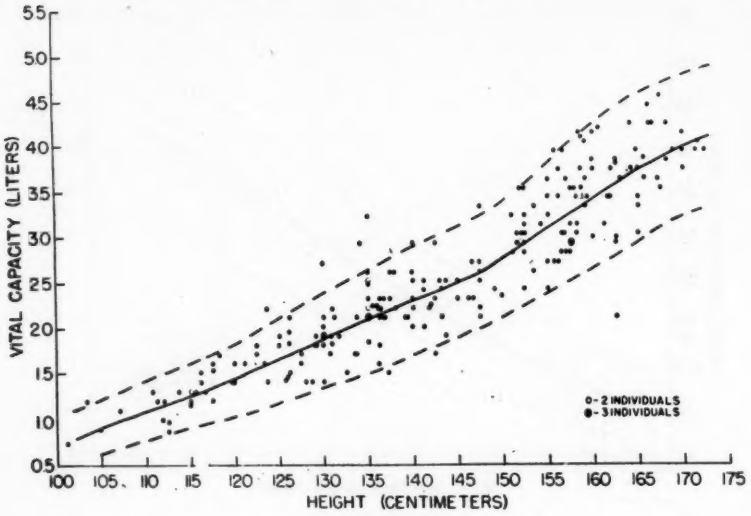

CHART 7

MAXIMUM BREATHING CAPACITY VS. HEIGHT
IN FEMALE CHILDREN AND ADOLESCENTS

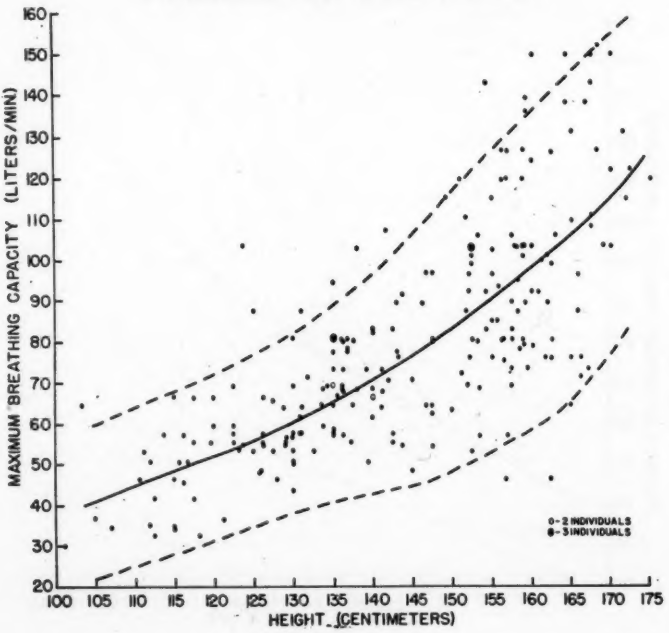

CHART 8

TABLE 9

PHYSICAL CHARACTERISTICS OF FEMALE CHILDREN AND ADOLESCENTS STUDIED

Age	No.	Av. Ht.	σ	Av. Wt.	σ
yr.		cm.	cm.	kg.	kg.
5– 5.9	11*	111.6	3.8	20.6	2.8
6– 6.9	8	120.7	8.1	23.0	2.9
7– 7.9	18	120.8	7.6	26.5	5.2
8– 8.9	19	129.5	4.0	30.8	5.0
9– 9.9	29	135.2	4.9	35.4	6.8
10–10.9	22	138.4	6.8	37.8	8.5
11–11.9	28	147.6	7.0	43.9	7.6
12–12.9	28	154.0	9.8	49.3	9.2
13–13.9	14	159.8	5.5	54.5	9.1
14–14.9	19	160.8	4.1	52.6	5.5
15–15.9	12	161.6	6.8	60.7	7.4
16–16.9	10	159.0	9.3	57.2	5.0
17–17.9	12	163.0	5.6	56.6	6.5
18–18.9	2	154.6	—	54.8	—

* Height and weight of one child was missed.

the 50 percentile line, and the weights, the 75 percentile. This indicates that this group was slightly heavier than the average but was of an average height. Since the group was drawn from an economic population probably above the average, the increased weight may reflect a higher caloric intake. The group, however, does not deviate significantly from a so-called "normal" female population of similar age, if the respective degrees of scatter are allowed for in the two populations.

The presently reported vital capacity values are about 10% greater than those reported by Baldwin.[5] This difference probably has a technical explanation, since Baldwin apparently did not correct volumes to BTPS; this, on the average, increases observed values 7 to 9%. Stewart's[3] vital capacity values are slightly greater than the present ones even though he did not correct volumes to BTPS; the reasons for this are not apparent. Emerson and Green's[6] vital capacity values are lower in a group which was much smaller than the present one. Their population generally was not as tall as the present one. When height alone is considered, however, a significant difference still exists. This has been discussed by Edwards and Wilson[7] who noted this discrepancy between Emerson and Green's results and their own early studies.[8] Edwards and Wilson felt this difference was due to different resistances of the spirometers. This is one explanation. The vital capacity measurements of Wilson and Edwards[8] are higher in the smaller children and lower in the larger children, as compared with the present results. This is probably because they calculated the average vital capacity per square meter of body surface over the entire age group from 6 to 16 years and assumed a linear relationship. The results of Turner and McLean[9] are hard to compare, since they pooled the results on males and females. The averages tend to be somewhat lower for both the vital capacity and the maximum breathing capacity when compared with observations on males.[1] They corrected their volumes to BTPS and used a similar type spirometer. There is close agreement between Turner and McLean's pooled vital capacity measurements and those reported here on females. In respect to the maximum breathing capacity the agreement is

TABLE 10

METHOD OF PREDICTING VITAL CAPACITY AND MAXIMUM BREATHING CAPACITY USING 4 ATTRIBUTES

		Vital Capacity (L)			Maximum Breathing Capacity (LPM)		
		Observed	Predicted	σ	Observed	Predicted	σ
Normal							
Age	13 yr.		3.49	0.68		104	19
Ht.	126 cm.		1.70	0.22		57	10
Wt.	48 kg.		3.02	0.42		87	20
B.S.A.	1.25 M^2		2.39	0.30		76	13
		2.50			61		
Kyphoscoliosis Secondary to Polio							
Age	15 7/12 yr.		3.66	0.39		105	23
Ht.	127 cm.		1.70	0.22		58	10
Wt.	23 kg.		1.40	0.25		53	10
B.S.A.	0.91 M^2		1.60	0.29		58	18
		0.38			16		

good except in the larger children. This is perhaps due to their treating the results as a linear function of height. When the degree of scatter in the two series are considered the differences are probably not significant.

In the older adolescent girls (16 through 18 years) there is good agreement between the presented results and the predicted female values of Baldwin et al.[10] and of West.[11] West's figures show better agreement in the smaller children since he based his predictions only on height or surface area. Baldwin et al. introduced an age correction factor in their regression equations which makes their values too high for the younger children.

The examples in table 10 demonstrate a recommended method of predicting the vital capacity or maximum breathing capacity. The healthy individual (not included in this series) is of an abnormal shape—that is, she is short in height and overweight. As a result, her predicted values on the basis of height are too low and those on the basis of weight are too high. Those predicted on the basis of age and body surface area show much better agreement with the observed value.

In the pathologic case the attributes are abnormal, and the case represents extreme

TABLE 11

CORRELATION COEFFICIENTS OF VITAL CAPACITY AND MAXIMUM BREATHING CAPACITY IN RELATION TO AGE, HEIGHT, WEIGHT AND BODY SURFACE AREA IN FEMALE CHILDREN AND ADOLESCENTS

	V.C.	M.B.C.	Age	Ht.	Wt.
M.B.C.	0.754				
Age	0.864	0.737			
Height	0.903	0.730	0.857		
Weight	0.847	0.685	0.823	0.883	
B.S.A.	0.888	0.708	0.852	0.944	0.965

Multiple correlation coefficient: V.C.=0.923
Multiple correlation coefficient: M.B.C.=0.754

respiratory disability. Her observed values are far below all the expected values minus two standard deviations. In addition this patient demonstrates the need for the use of all four attributes. If her prediction was made on the basis of age alone, she would be penalized for her small size. When this small size is taken into consideration her observed values are abnormally low.

Whitfield et al.[12] have demonstrated in adults that the use of multiple attributes to predict the vital capacity is better than the use of only one. In order to test this in children, a similar analysis of multiple correlations was carried out on the present data.

Table 11 presents the correlation coefficients for the vital capacity and maximum capacity in relation to age, height, weight, and body surface area in female children and adolescents. Each of the individual attributes showed a high positive correlation. These correlation coefficients have in part been influenced by the wide range from which this population has been drawn. When all the attributes (age, height, weight, and the surface area) are employed only a slight improvement in the predictability results.

The above examples emphasize that, in the abnormally shaped individual, as a tall thin person, or a short fat person, the use of all the above attributes should give a truer value. If the individual has an average size and configuration the use of any one of these attributes would predict adequately the expected vital capacity or maximum breathing capacity. Even in this instance the use of all four attributes as a basis for prediction will give more stability to the finally predicted value.

Summary

Expected mean values and a range of normal values (plus or minus twice the standard deviation) are presented for the vital capacity and the maximum breathing capacity of female children and adolescents.

Although multiple correlation does not demonstrate a particularly higher degree of predictability it is recommended that the above values be based upon the four attributes (age, height, weight, and body surface area) rather than upon a single attribute. This is especially important in the abnormally shaped individual.

Acknowledgments

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Miss N. Koohtow performed the calculations for the multiple correlations and Miss L. Servello delineated the figures.

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SPANISH ABSTRACT

Capacidad Respiratoria Máxima y Capacidad Vital en Niñas y Adolescentes del Sexo Femenino

Este estudio se hizo a fin de obtener cifras de la capacidad vital y capacidad respiratoria de niñas y adolescentes, realizándose en escolares de la vecindad de Boston en un total de 233 muchachas con edad variable de 5 a 18 años. Ambas capacidades respiratorias se midieron con el aparato de Benedict-Roth.

La capacidad vital se define como la expiración máxima después de la inspiración máxima.

En las gráficas adjuntas al trabajo se presentan los resultados obtenidos. Al contrario de las observaciones hechas en niños adolescentes no se observaron en estas niñas cambios notables durante el período de crecimiento rápido de la adolescencia. La diferencia observada por los autores con las observaciones de otros señalados en el artículo, las consideraron debidas a que los actuales correlacionaron la edad, el peso, la estatura y la superficie corporal para las determinaciones finales, conducta que no se ha seguido por los otros y recomiendan que siempre se tomen en cuenta los 4 factores, en particular cuando los individuos estudiados tienen anormalidades físicas.

55 Shattuck Street

TOTAL AMINO ACID COMPOSITION IN MATURE HUMAN MILK

Analysis by the Ion Exchange Resin Column Chromatographic Technic

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IF HUMAN milk is to serve as the pattern of nutriments best suited for rapidly growing infants, precise knowledge of its composition is of great importance. This would be specially true for amino acids which are the building blocks of body proteins. Literature pertaining to amino acid content in mature human milk proteins shows widely divergent values.[1] It is conceivable that this variability is partly due to differences in age, parity, individual nutritional and genetic factors and duration of lactation of the donors; and partly due to the procedures of collection, preservation, hydrolyses and, above all, to differences in the methods of analysis. All previous analyses have been by microbiologic technics or by utilizing a chemical procedure specific for a given amino acid. Neither of these methods is suitable for detecting unsuspected amino acids which might be present in human milk, perhaps making it uniquely suitable for infants. The recent recognition of a specific "growth factor" in human milk[2] probably exemplifies a fruitful search for this possibility. The purpose of this study is to investigate the total amino acid composition (free and protein amino acids) of pooled human milk utilizing the sulfonated polystyrene resin (Dowex-50) column chromatographic technic of Moore and Stein.[3] This method should enable one to detect all amino acids and ninhydrin-reactive related compounds present, as well as to provide comparative data on the microbiologic and chromatographic methods for quantitative determination of amino acids.

MATERIALS AND METHODS

Analyses were carried out on the milk of 14 women of whom 12 were Puerto Rican and 2 were non-Puerto Rican white of similar socio-economic status. At the time of milk collection, all mothers were in good physical health and clinically showed no signs of malnutrition. The rate of weight gain of each infant was considered satisfactory. The donors ranged in age from 19 to 28 yr.; in parity from i to iv and the duration of lacation was 4 to 10 wk. postpartum.

From each donor, samples of about 15 cc. milk were collected from both breasts, mixed and immediately frozen until used. Equal volumes were taken from samples from 9 mothers to make up Pool A and from 5 different mothers for Pool B. An amount of pooled milk was weighed into a small container, and both milk and container were dropped into the flask for digestion and total nitrogen determination by the semimicro Kjeldahl method.[4] The value for total solids was obtained by drying to constant weight in vacuo over sulfuric acid.

Acid Hydrolysis: The milk was refluxed with twice its volume of approximately 6 N. HCl for 26 hr. at 120°C. The hydrolysate was filtered to remove the insoluble material, washed and the excess acid in the filtrate removed by concentration in vacuo. The syrupy hydrolysate was made up to volume (approximately 1 cc. $\simeq$ 0.5 cc. milk) with the appropriate citrate buffer prior to being placed on the resin column. The total nitrogen of this hydrolysate solution was again determined.

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Usually 1 cc. hydrolysate was added to the resin column and the operation of analysis carried out as described by Moore and Stein.[3]

Alkaline Hydrolysis: Since tryptophan is known to be destroyed by hot mineral acids especially in the presence of carbohydrates,[5] an alkaline hydrolysate was prepared for its determination.[6] Milk was autoclaved with 3 times its volume of 6 N. NaOH for 16 hr. under 15 lb. pressure. The hydrolysate was filtered, washed, adjusted to a pH of 4.5-5.0 by HCl and made up to desired volume. Analysis was done as soon as possible to prevent loss during storage. The recovery of known amounts of tryptophan added before or after hydrolysis was found to be 90% and 100%, respectively. Probably the 10% loss of the tryptophan added before hydrolysis was due to the presence of large amounts of carbohydrate, or perhaps there was no loss since the value is within the experimental error of the author's method.

Results

Identification of the substances responsible for the various peaks in the chromatogram has been aided by the use of paper chromatography. The even numbered fractions were first analyzed by the ninhydrin method to locate peaks. The odd numbered fractions comprising the peak points were then desalted by the device of Consdon et al.[7] and chromatographed according to the technic of Dent.[8, 9]

TABLE 1

	Pool A		Pool B	
Total N of Milk (mg./cc.)	2.16		2.21	
Total N of Hydrolysate (mg./cc.)	1.04	0.935	0.97	
Total Solid in Milk (gm./100 cc.)	12.75		12.96	
Total Amino Acids*	mg./16 mg. Total Nitrogen†	mg./100 cc. Milk†	mg./16 mg. Total Nitrogen	mg./100 cc. Milk
Aspartic acid	8.39	113.2	8.08	111.8
Threonine	4.26	57.4	4.20	58.1
Serine	4.04	54.3	4.22	58.3
Glutamic acid	12.75	165.5	13.55	187.2
Proline	7.00	94.2	6.57	90.8
Glycine	2.20	29.6	2.24	31.0
Alanine	3.67	49.4	3.47	47.9
Cystine	0.92	12.5	1.09	15.1
Valine	5.07	68.2	4.78	66.0
Methionine	1.14	15.4	1.04	14.3
Isoleucine	4.31	57.9	3.94	54.4
Leucine	8.67	116.7	9.00	124.2
Tyrosine	2.40	32.3	3.31	45.7
Phenylalanine	3.66	49.3	2.99	41.2
Tryptophan‡	1.28	17.2	—	—
Histidine	2.65	35.8	2.19	30.2
Lysine	8.16	110.5	7.17	99.0
Arginine	4.18	56.4	3.67	50.6

* Total amino acids = free amino acids + amino acids from milk protein.

† The amino acid results for Pool A are the average of 2 complete analyses of 2 hydrolysates.

‡ Average of analyses of 3 alkaline hydrolysates.

Although it is known that total amino nitrogen constitutes only about 85.6% of total nitrogen, the results are expressed on the basis of total nitrogen of whole milk because the free as well as protein amino acids were measured. To render the data comparable to reported values in literature, they are calculated from the nitrogen contents of hydrolysates and whole milk to amounts per 100 cc. whole milk as shown in table 1.

The chromatograms of acid hydrolysates of human milk on the Dowex-50, 15 × 0.9 cm. column[3] revealed a distinct ninhydrin-positive peak which emerged immediately before histidine. Stein[10] designates this component as "X" and it has recently been identified as 3-methyl histidine.[11] It was found to be present in these milk preparations in amounts approximately equal to 0.202 mM uncorrected leucine equivalent[12] per 100 cc. whole milk.

In the acid hydrolysate of whole human milk, three unidentified ninhydrin-reactive components were encountered. The first one appeared as a symmetric peak "I" between valine and methionine in the chromatogram of the 100 × 0.9 cm. resin column. The amount present was approximately 0.295 mM uncorrected leucine equivalent per 100 cc. whole milk. When the peak fractions were pooled, desalted and investigated on Phenol-"Collidine" filter-paper chromatograms[8] it appeared as a single spot with the behavior similar to glucosamine or galactosamine. A second unidentified symmetric peak "II" emerged about 40 cc. after phenylalanine in the chromatogram of the 100 × 0.9 cm. resin column. Whole milk contains about 0.11 mM uncorrected leucine equivalent of this constituent per 100 cc. On filter-paper chromatograms it appeared as a single spot and behaved similarly to glucosamine or galactosamine and coincided with added glucosamine. Neither of these two unidentified peaks is in the position on the resin column chromatogram where glucosamine is said to be.[10] Therefore the identity of these two ninhydrin-reacting substances is not clear. Apparently neither is glucosamine nor are they any of the other substances identified by Dent,[8] with the possible exception of galactosamine.[13]

The third unidentified component "III" emerged as a skewed peak immediately after the tyrosine and phenylalanine peak in the chromatogram of the 15 × 0.9 cm. resin column. It is present only in minute amounts and therefore not available for study by the filter paper method. However, its relative position on the chromatogram suggests that it may be composed of β-alanine and β-amino isobutyric acid.[10]

Comment

If one takes into consideration the differences in methods of preparation and analysis, the author's analytic data are in good agreement with those of Plimmer,[14] Beach,[15] Williamson,[16] Block [17, 18] and Macy[19] with the exception of glutamic acid, cystine, tyrosine and glycine. The authors have no explanation of the low glutamic acid content as compared with that of Williamson's value.[15] The low cystine content might be due to its relatively low solubility in aqueous solution or its destruction during hydrolysis in the presence of carbohydrates.[20] The latter reason might also account for the low and variable tyrosine value.[21] Glycine was found to be present in human milk in amounts as indicated in table 1.

Identification of the two unknowns, "I" and "II," merits further study because they are present in significant amounts in whole human milk. It has been shown that normal infants fed a diet composed of L-forms of amino acids in approximately the same composition as human milk[22] will grow at the usual rate without addition of 3-methyl histidine and the two unknowns. Therefore, at least by inference from these short-term

observations, they cannot be considered as "essential" constituents of infant diet, although they may have some role in the nutrition of infants.

Summary

Values for total amino acids in two pools of mature human milk, consisting of milk from 9 and 5 individual mothers, have been determined by the ion exchange resin column chromatographic technic.

3-methyl histidine and two unidentified ninhydrin-reactive substances are found to be present in significant amounts in whole human milk.

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SPANISH ABSTRACT

Composición en Amino-ácidos de la Leche Humana

Si se acepta que la leche humana es la más adecuada para los niños, es de gran importancia el conocimiento de su composición, en particular por lo que respecta a los amino-ácidos, considerados como la base de las proteínas corporales. Los numerosos estudios al respecto muestran valores muy divergentes; esta variabilidad se debe en parte a las diferencias en edad, factores genéticos y nutricionales, individuales, etc. de las mujeres, así como a los procedimientos de la recolección, preservación, métodos de análisis, etc. de las leches. El presente trabajo se dedica a investigar la composición total en amino-ácidos por el método cromatográfico de Moore y Stein, de la leche de 14 mujeres (12 portorriqueñas y 2 blancas), en buen estado de salud, y clínicamente sin signos de desnutrición; los hijos de estas mujeres aumentaban de peso satisfactoriamente. La edad de las donantes varió de 19 a 28 años; amamantaban a sus niños en el período comprendido de 4 a 10 semanas después del parto.

En términos generales la composición de la leche estudiada por estos autores estuvo de acuerdo con los datos de otros, excepto en lo que respecta al ácido glutámico, cistina, tirosina y glicina, encontrados con valores más bajos. Se aislaron tres elementos más a los señalados clásicamente: la 3-metil histidina y dos substancias no identificadas reaccionantes a la ninhidrina, todas en cantidades significativas. Según las observaciones hasta la fecha, parece ser, para estos autores, que tales substancias no se pueden considerar en la dieta infantil como elementos esenciales aunque deben tener cierto papel en la nutrición de los lactantes.

477 First Avenue

HYPERTENSIVE PHASE OF ACUTE NEPHRITIS

Specific Therapy with a Derivative of Veratrum Viride

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VERATRUM derivatives have proved of value in the control of certain acute hypertensive states in adults.[1,2] This suggested that their usefulness might be extended to the acute phase of childhood nephritis, particularly in the prophylaxis of myocardial failure and encephalopathy. During the past two years a veratrum derivative alkavervir* has been given to six children in the hypertensive phase of acute nephritis. A prompt hypotensive effect was observed in each instance. The following case histories illustrate some of the results of this therapy.

CASE HISTORIES

Case 1. J. L. Encephalopathy, convulsions, moderate hypertension.

This 12 yr. old Mexican boy entered the hospital in a semicomatose condition. Three weeks before he had apparently made an uneventful recovery from scarlet fever, although he occasionally complained of a persistent headache. Forty-eight hours before admission he began to vomit, and on the morning of entry had a convulsion. Intermittent convulsions lasted 8 hr. and were accompanied by cyanosis. Initial physical examination showed a disoriented, combative boy with moderate generalized edema and a blood pressure of 180/130 mm.Hg. Heart was enlarged to percussion and on roentgen examination a widened cardiac shadow was seen. Electrocardiogram was normal. Urine was grossly bloody, contained red blood cell casts, and gave a strongly positive reaction for albumin. Blood NPN was 113 mg./100 cc. During the 1st 4 hr. on the ward he remained out of contact and belligerent, and had periodic convulsions of a tonic-clonic pattern. Blood pressure stabilized at 170/120 mm.Hg. At this time veriloid® was given intravenously, and 20 min. later he became responsive and cooperative. Blood pressure was 140/100 mm.Hg. Two hours later he fell asleep, coinciding with a blood pressure of 120/90. During maintenance (*vide infra*) veriloid® therapy continued over a total period of 12 hr., the blood pressure stabilized at 130/90 mm.Hg. The following day the NPN was 54 mg./100 cc. and he began to lose weight. Blood pressure readings are recorded in chart 1. Recovery was without incident, and 2 yr. following his illness he showed normal urinary findings and blood pressure.

Case 2. L. S. Myocarditis with failure.

This 7 yr. old Mexican boy entered the hospital with signs of acute cardiac failure. Two weeks before entry he had an attack of acute pharyngitis, followed 1 wk. later by swelling of the face, abdomen and scrotum. Thirty-six hours before entry he became dyspneic, 12 hr. later was orthopneic, and on the morning of admission was cyanotic. Initial examination showed a deeply cyanotic boy with generalized edema, orthopnea and a blood pressure of 160/120 mm.Hg. He seemed acutely uncomfortable. Heart was enlarged to percussion, and the heart rate ranged from 160 to 180. Roentgen examinations of the chest were consistent with pulmonary congestion. Electrocardiogram was grossly abnormal. Albumin, red blood cells, and red blood cell casts were found in the urine. NPN was 58 mg./100 cc. On entry the boy was given digitalis and after 6 hr., during which time his blood pressure stabilized at 155/120 mm.Hg, veriloid® was started intravenously. There was a rapid fall in blood pressure with levelling off at 100/80 mm.Hg (chart 2). After 9 hr. veriloid® was discontinued. During the next 4 days his edema subsided, with a loss of 3.6 kg. body weight. Heart returned to normal size and recovery was uneventful.

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* Veriloid®, NNR, Riker Laboratory, Los Angeles.

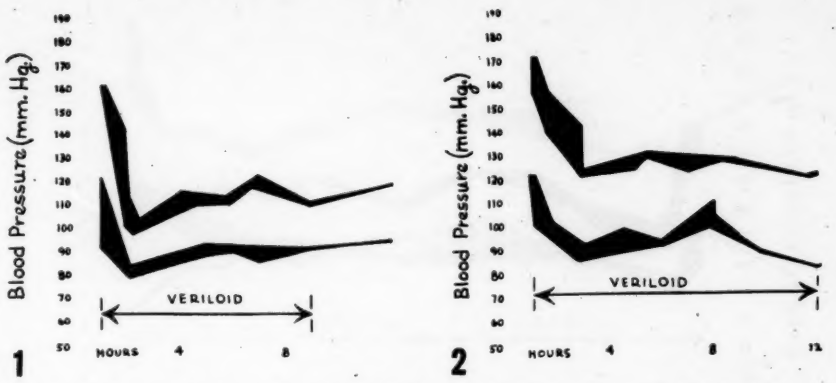

CHART 1. Patient J. L. Aged 12 yr. Male. Disoriented and combative. During veriloid® administration began to respond, then fell asleep at low point of blood pressure readings, 2 hr. after veriloid started.

In presenting these data on blood pressure method outlined by Blaney[8] has been followed. Range of blood pressure readings is shown by broad line representing 4 or more determinations of systolic and diastolic pressures.

CHART 2. Patient L. S. Aged 7 yr. Male. Cardiac failure and pulmonary congestion. Prompt hypotensive action noted 45 min. after veriloid® started. After drug was discontinued BP climbed to 130/105, then gradually dropped to normal levels over 4 day period.

Case 3. G. S. Anasarca, cardiac enlargement, pulmonary edema.

This 4 yr. old girl entered the hospital because of generalized edema. Two weeks before admission the child had received penicillin for a mild sore throat; subsequently she had been well until 4 days before entry when abdominal swelling was observed. Two days later she became markedly short of breath. On initial examination the child seemed acutely ill and dyspneic. Blood pressure readings stabilized at 150/120 mm.Hg during 6 hr. of observation. There was abdominal distention with evidence of chest compression by the high diaphragm. Films of the heart showed an enlarged cardiac silhouette and vascular shadows consistent with pulmonary engorgement. Gross hematuria was noted, and red blood cell casts were found on microscopic examination of the urinary sediment. NPN was 52 mg./100 cc. Veriloid® administration was followed by a prompt drop of the blood pressure at 115/90 mm.Hg (chart 3). During the next 8 hr. the child seemed more comfortable and the chest cleared. Grossly abnormal urinary findings were observed for a period of 10 days, recovery thereafter was without incident.

Case 4. V. L. Severe hypertension with headache as the only symptom.

This 13 yr. old Mexican boy entered the hospital with the complaint of a severe headache of 1 wk.' duration. Over the same period he passed grossly bloody urine, and some swelling of the face was noted. On initial examination he appeared mildly edematous and orthopneic. His blood pressure stabilized at 185/120 mm.Hg. Positive urinary findings included red blood cell casts and albumin. NPN was 46 mg./100 cc. Because signs and symptoms were mild he was treated by barbiturate sedation alone for the next 4 days. On this regimen he remained fairly comfortable, but the headaches continued and the blood pressure fluctuated between 190/120 and 170/100 mm.Hg, never falling below the latter figure. On the fourth day veriloid® was started; within 2 hr. the blood pressure fell to 130/80 mm.Hg, and eventually stabilized at 140/95 mm.Hg on maintenance therapy (chart 4). Coinciding with this was a disappearance of headache. Veriloid® was discontinued after 22 hr. and recovery thereafter was uneventful.

Case 5. A. A. Minimal signs with severe hypertension.

This 6 yr. old Mexican boy entered the hospital because of dyspnea and vomiting. One month before he had a mild sore throat which subsided uneventfully. This was followed 2 wk. later by swelling of the face and, a few days afterwards, by headache. On entry he was an alert and cooperative boy with mild facial edema and evidence of ascites. Blood pressure was 210/130 mm.Hg.

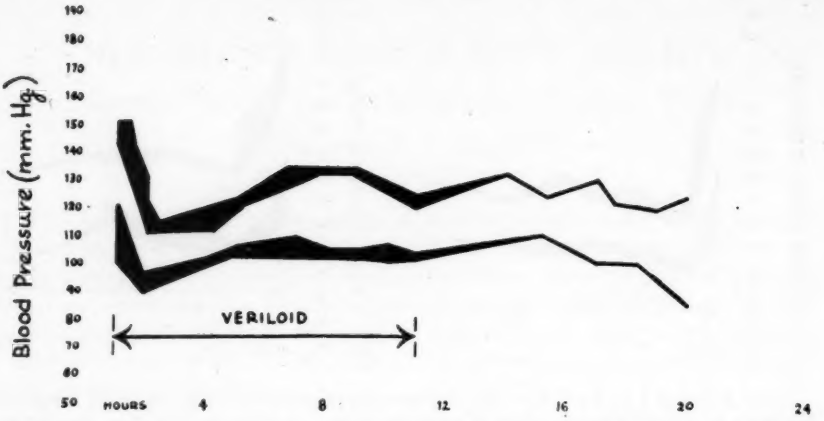

CHART 3. Patient G. S. Aged 4 yr. Female. Cardiac failure and pulmonary edema. Following veriloid® BP dropped rapidly, ranging between 105/90 and 135/100 on maintenance therapy, then gradually returned to normal levels without showing "escape" phenomenon.

A moderate degree of arteriolar constriction was noted in the retinas, physical findings otherwise were not remarkable. Urine was grossly bloody, contained albumin, free red blood cells and red blood cell casts. Chest RG, ECG and NPN showed no essential deviation from the normal. Blood pressure stabilized at 190/135 mm.Hg during the 1st 24 hr. on the ward. One day after admission veriloid® was started, with the sequence of events shown in chart 5. Forty-eight hours later, after veriloid® was discontinued, blood pressure rose to 170/120 mm.Hg. At this time he was given magnesium sulfate, and an almost identical response was obtained.

Case 6. J. H. Recurrent convulsion.

This 12 yr. old Mexican boy was admitted to the hospital because of a prolonged, generalized convulsion. One month before entry he had been febrile, complained of a severe sore throat and large painful swellings involving both sides of the neck. These masses diminished during the next 2 wk. and the boy was well until the day before entry when he lost his appetite, vomited several

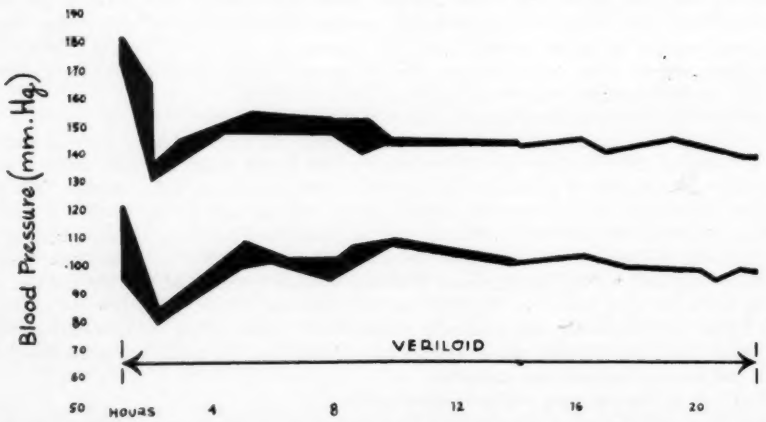

CHART 4. Patient V. L. Aged 14 yr. Male. Uncomplicated hypertension. Prompt drop in BP following veriloid® infusion, maintenance at mildly hypertensive levels for 22 hr., then gradual fall to normal.

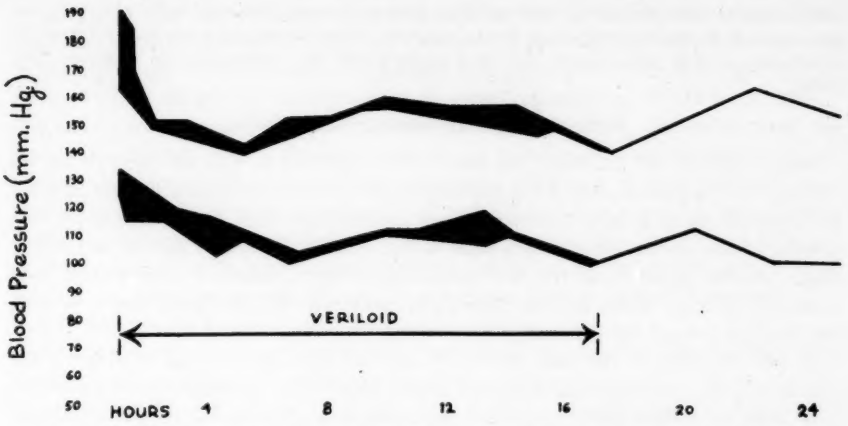

CHART 5. Patient A. A. Aged 6 yr. Male. Severe hypertension without complications. Shows "escape" phenomenon following cessation of veriloid® therapy.

times, and complained of head pain. Four hours before coming to the hospital twitching movements of the facial muscles were observed. Shortly afterwards he had a major convulsion lasting 30 min. He then convulsed intermittently for the next 2 hr. On initial examination the boy was restless and only semiconscious. Occasional twitching movements of the face and extremities were noted. Blood pressure stabilized at 170/130 mm.Hg. Urine was bloody, contained many red blood cells, red blood cell casts, and a large amount of albumin. NPN was 42 mg./100 cc. During the first day on the ward he became more responsive, but remained lethargic and irritable and continued to complain of headache. Over this 24 hr. period he remained hypertensive; by the following day the blood pressure had risen slightly to 190/140 mm.Hg. Veriloid® was given intravenously at this time. A prompt hypotensive episode occurred (chart 6). After 22 hr. veriloid® was discontinued. By this time the patient was quiet and cooperative, and stated that his headache was gone. He was sent home on the seventh day, and followed thereafter in clinic. He has been well, and normotensive, on subsequent study.

No objective evidence of toxicity from the therapy was encountered and no side effects other than

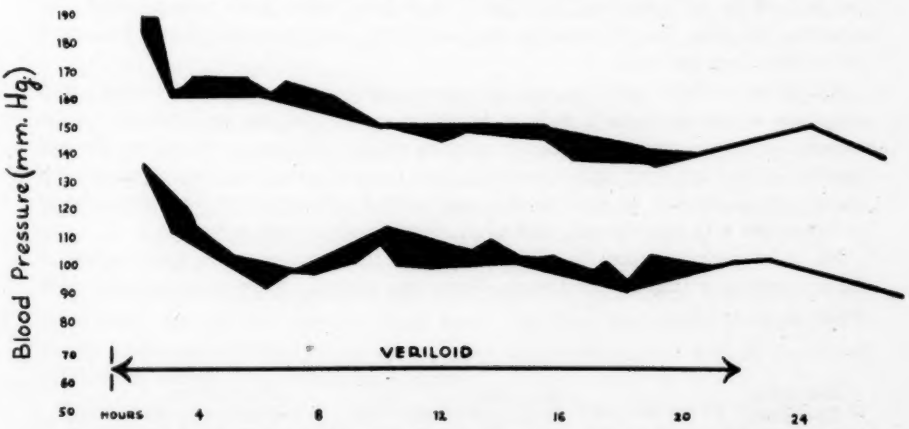

CHART 6. Patient J. H. Aged 12 yr. Male. Prompt hypotensive response with initial veriloid® infusion, then gradual drop in BP maintained after veriloid® was discontinued.

mild nausea (Cases 4 and 6) or vomiting (Case 1) were observed. The renal and cardiac status did not appear to be affected unfavorably by the treatment. These patients have now been followed for a minimum of 2 yr. after illness: they have remained well and normotensive on numerous clinic visits.

Problems of the Hypertensive Phase

Acute nephritis of childhood has shown little variation in incidence despite the increased use of antibiotics early in the treatment of streptococcal infections. Figures collected by Goettsch[4] show a fairly constant disease rate through many cycles of therapy. The severity of the disease when it does occur is still great, and children still die in its early stages. At the present time the two complications which contribute most to this early mortality are heart failure and encephalopathy: both may be partially, or almost entirely, the result of a rapid rise in blood pressure.

In the treatment of the early phases of acute nephritis the cardinal objective is the prophylaxis of myocardial and cerebral damage. Myocarditis, even myocardial infarction, may occur in normotensives, but when hypertension supervenes the danger of organic myocardial lesions, leading to failure, and possibly to permanent heart damage, is greatly increased. There is also the ever-present threat of encephalopathy when the blood pressure rises quickly and steadily to exceedingly high levels. That the risk to life in acute nephritis is not proportional to the urinary findings is clearly stated in the frequently quoted dictum of Volhard: "In the early stage, it is the damage to the heart which is of first and highest importance. The danger to the brain is second, and to the kidneys only third."[5] The relative roles played by myocarditis and by hypertension in precipitating cardiac failure may always be debatable. It seems clear, however, that acute hypertension is likely to be deleterious to the heart and to the brain of the sick child.

The problems of the hypertensive phase have been clearly defined by numerous studies: originally by Goodhard,[6] later by Rubin,[7] McIntosh[8] and Butler.[9] The mechanics of the increase in blood pressure are clear, and the effects of hypertension on the heart and brain have been well established. But specific therapy for the hypertensive phase remains difficult, and the need for hypotensive therapy remains ill-defined. This is apparent from the multiplicity of agents and therapeutic procedures which have been suggested for control of this brief, crucial, interval in the course of the acute nephritic patient. The search for an ideal agent continues.

The agent of choice might be described as one which: (a) controls the factors which contribute to cardiac failure, such as hypertension, myocarditis, and reduced cardiac output; and (b) reduces or reverses the factors which contribute to encephalopathy and possible cerebral accidents, such as cerebral edema, cerebral vasospasm and increased intracranial arterial pressure. In addition, this agent should not have severe side effects, should be compatible with digitalis and, most of all, should work quickly and safely.

No one hypotensive agent has consistently filled these criteria, as the great variety of drugs currently or formerly used attests. Some idea of their variety is apparent from the following partial list:

Hypotensive Agents Used in Acute Nephritis

benzazoline	hydrazaline	protoveratrine
dibenamine	magnesium sulfate	tetraethyl ammonium salts
dihydroergocornine	nitrites	thiocyanate
hexamethonium bromide	novacaine	veratrum viride

Certain of these agents are, at least theoretically, more desirable than others. Some have been virtually abandoned, others are used only sporadically, and only a few are used frequently to control hypertension in childhood. An example of the latter type is magnesium sulfate, first used intravenously in acute nephritis by Blackfan in 1923.[10] Magnesium sulfate remains the most frequently used medication, despite its many disadvantages. Among these is the insufficient margin of safety between the effective hypotensive serum level and the level which produces a depression of respiration and myocardial function. Magnesium sulfate enjoys alternating periods of popularity and disfavor, depending most often on personal experience with the drug. But the primary objection to its routine use is its unpredictable effect on children with the hypertension of acute nephritis. In a high percentage of cases (in some series 50% or more) magnesium sulfate fails to demonstrate any appreciable hypotensive effect.

Among the other compounds used in the treatment of hypertension several of the newer drugs deserve mention. Hexamethonium is a potent depressor agent but shares the disadvantages of other ganglionic blocking agents in that it produces postural hypotension and various side effects due to its extensive autonomic blockade. Because of the severe visual disturbances and urinary retention which may follow its use, it is probably not the agent of choice for these patients. Furthermore, the presence of renal damage is regarded by Grimson[11] as a contraindication to the drug. Hydrazaline (apresoline®) is a less effective hypotensive agent, and its side effects of headache, palpitation, tremor and anxiety mitigate against it. Although the latter drug is a potent vasodepressor, Kvale[12] has shown that it has the same disadvantage as magnesium sulfate—an unfavorable effect on the cardiovascular system.

Veratrum Preparations

Although no hypotensive agent currently available is ideal, the derivatives of veratrum viride show the most promise at the present time. Of all the hypotensive agents used, veratrum has been by all odds the most effective, and, in the crude preparation, the most difficult to handle. One early chapter in its long and colorful history was contributed by pediatrics: The first recorded use of veratrum on a child was in the therapy of worms. Some time later its effectiveness as a vermifuge was concisely summed up by these words: "Where it kills not the patient it would certainly kill the worms—but the worst of it is it will sometimes kill both."[13]

Recently several purified preparations of veratrum viride have been made available. Though the theoretic advantage might seem to lie with protoveratrine, Swiss[14] has shown that its actions may not strictly parallel those of the more familiar preparations. Klohs[15] has also demonstrated that some of the protoveratrine preparations in use are actually inconstant mixtures of alkaloids. Hence in this clinic the standardized mixture of alkaloidal esters marketed as alkavervir* was adopted.

The effects of veriloid® may be summarized as follows:

1. Hypotensive—The hypotensive effect is achieved by generalized vasodilation. This is mediated through the central nervous system, the drug has neither a sympatholytic nor an adrenergic blocking action. The patient is maintained in a state of circulatory equilibrium, but at a lowered arterial pressure.

2. Myocardial—Following veriloid® administration Wilkins[1] has shown that there is an increase in cardiac output, and bradycardia. The latter is not causally related to the hypo-

* Veriloid®.

tension but is vagal in origin, being abolished by vagotomy or atropine. Electrocardiographic changes consist of reversal of the strain pattern during veriloid®-induced hypotension. Since the drug has been used, by Kauntze et al.[16] in the therapy of congestive and hypertensive failure in adults, and given freely to patients already digitalized, it was anticipated that a protective effect on the heart might be found. This is in direct contrast to magnesium sulfate which has a cardiac depressant effect.

3. Renal—The renal bed shares in the generalized vasodilation which follows administration of the drug. This results in an initial decrease of renal blood flow followed by a quick return to the normal or above normal values. The urine output reflects this initial decrease; Goldman[17] has shown that a smaller volume of urine is produced during the period of hemodynamic adjustment to the lower pressure.

Materials and Methods

Veriloid® may be administered by the oral, intramuscular or intravenous routes. Inasmuch as these patients are usually nauseated and may be vomiting, and since close control over initial dosage is desirable, intravenous administration is usually preferred. On admission the patient is observed for from 2 to 12 hr. on the ward; during this time symptoms, behaviour and evidences of encephalopathy are recorded. Baseline blood pressure readings are made, an ECG is obtained, and blood is drawn for the NPN determination. Indications for the use of hypotensive agents are considered to be a systolic pressure of 160 mm.Hg and/or a diastolic pressure of 100 mm.Hg or more; or lower blood pressure levels if there is evidence of heart failure or cerebral symptoms. The following regimen is suggested:

Dosage: Veriloid® administration (intravenously) consists of 2 phases: an initial, fairly rapid infusion followed by a slow intravenous drip.

Initially: Give 0.022 cc. veriloid solution/kg. body weight over a period of 20 min. This amount is diluted to a volume of 10 cc. with 5% glucose solution

e.g., The patient weighs 20 kg. 0.022 cc. $\times$ 20 = 0.44 cc. veriloid® diluted to 10 cc. in a 5% glucose solution

a. The injection should be made at the rate of ½ cc. of this diluted solution/min. for 8 min. with continuous observation of blood pressure. (Total 4 cc.)

b. Wait 2 min.

c. Continue at the rate of ½ cc./min. for 6 more min. watching blood pressure closely. (Total 7 cc.)

d. Wait 2 min.

e. Continue at the rate of ½ cc./min. for 6 more min., watching blood pressure closely. This will exhaust the supply in the syringe. (Total 10 cc.) If, after a 15 min. interval, the blood pressure is not lowered to the desired level, repeat whatever part of a similar 10 cc. preparation that may be required to bring the BP to the level desired. Always stop when a 20 mm. fall is observed, and wait until the BP levels off before continuing.

Maintenance: Start a slow IV infusion using 5% or 10% glucose as the diluent. Give 0.13 cc. veriloid®/kg. body weight, in total solution of 22 cc./kg. body weight. Run at rate of 5 drops/10 kg. body weight/min.

e.g. With a 20 kg. patient 0.13 cc. veriloid® $\times$ 20 = 2.6 cc., veriloid® to be added to 20 $\times$ 22 cc. = 440 cc. of a 5% glucose sol. given at rate of 2.0 $\times$ 5 drops = 10 drops/min.

Blood pressure must be taken and recorded every 15 min. while this maintenance infusion is running. It may be set up to run 15 to 20 hr. if necessary.

Further medication with veriloid® should be determined on the basis of subsequent episodes of hypertension. After the initial infusion and maintenance dosage the patient may "escape" from the effects of the drug, and the blood pressure climb to near the initial levels. A second maintenance infusion may then be used.

Overdosage results in extreme hypotension with eventual collapse, bradycardia, and cardiac irregularities. These complications are rare, but to relieve them there must be at the bedside of each patient receiving the drug:

1. One ampule of ephedrine 1% to control extreme hypotension.

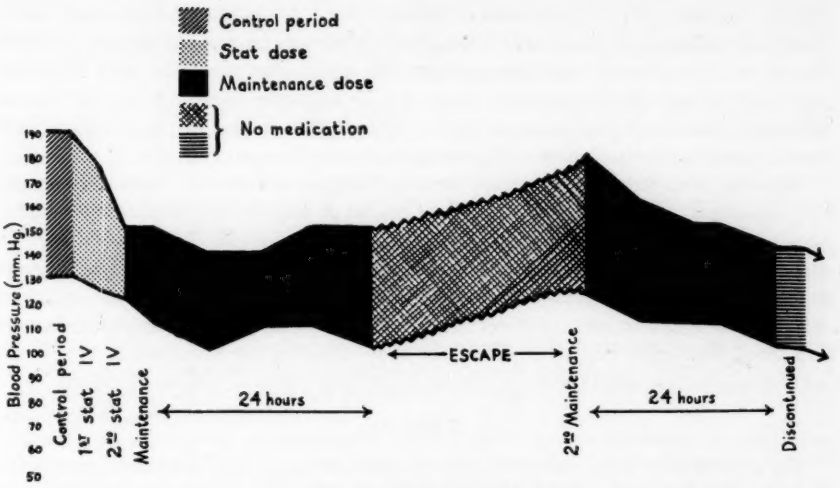

CHART 7. Characteristic response of hypertensive nephritic patient to suggested regimen of stat and maintenance veriloid® therapy.

2. Atropine solution 1:1000 for IM or IV use to overcome extreme bradycardia.

It was found that the blood pressure could be reduced to a selected level, or to normal or subnormal levels, by changing the rate of the infusion. In general, no attempt was made to produce normal or hypotensive levels since a fall of only 20 or 20 mm.Hg was often sufficient to relieve encephalopathy and reduce the hypertensive strain on the patient. A detailed chart of a characteristic response is shown in chart 7.

COMMENT

Since the blood pressure of a healthy child, as well as of one with acute hypertension, is naturally quite variable, much skepticism is justified in reviewing the significance of any lowering consequent upon a therapeutic procedure. Under conditions of hospitalization there are numerous factors which apparently affect the child's blood pressure, whether or not the child has an illness ordinarily associated with hypertension. The effects of separation from parents, painful procedures, and other conditions incident to the hospital milieu have recently been reviewed by Clayton.[18] This report augments the skepticism with which all blood pressure studies—including this one—must be regarded.

A second important consideration is that the blood pressure of a child with acute nephritis may be lowered in a variety of ways by a number of different hemodynamic and physiologic adjustments. But before undertaking this procedure in any individual case it is well to ask whether, in the given situation, the pressure needs to be lowered at all. In the asymptomatic cases there is no competent evidence that hypertension sustained for only 3 to 4 days is deleterious (e.g., Case 4). Similarly the height of the blood pressure frequently bears little relation to the severity of signs or symptoms. The sickest children in this small group were Cases 1 and 2; their blood pressure levels ranged 20 to 50 mm.Hg below the level of Patients 4 and 5, who were only mildly ill.

If prompt and effective control is necessary, the natural history of the acute hypertensive phase suggests that it is needed for only a short period, usually not exceeding 96 hours.

Only a remission of the hypertension is required. A fall to normal blood pressure values is neither desirable nor necessary. When the possibility of myocardial damage, cerebral damage or, rarely, severe renal damage is present, every effort should be made to reduce the blood pressure by the quickest, most effective and safest means. From this limited series only limited conclusions may be drawn. These studies suggest that veriloid® therapy may be useful in the treatment of hypertension incident to acute nephritis.

Extensive adult studies, particularly those by Wilkins[1] and Moyer,[2] further strengthen this impression. In adult patients with severe benign or malignant hypertension veriloid® shows promise of being the most effective agent presently available. When it is desired to reduce the blood pressure quickly, as in an acute hypertensive crisis, veriloid® seems to be the drug of choice. In acute nephritis it is not the ideal agent, but its ability to reduce peripheral resistance, to lower blood pressure quickly, to maintain cardiac output and blood flow in the various organs of the body, including the brain, at adequate levels without undue side effects make it worthy of extensive clinical trial in childhood.

Summary

The hypertensive phase of acute nephritis remains crucial and difficult to control. In a small series of cases prompt remission of hypertension and accompanying complications occurred following the use of a derivative of veratrum viride.

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SPANISH ABSTRACT

La Fase Hipertensiva de la Nefritis Aguda—Tratamiento Específico con un Derivado del Veratrum Viride

Los derivados del veratrum se han empleado eficazmente en los adultos para algunos estados hipertensivos agudos; de aquí que se pensara administrarlos en la nefritis de la infancia preferentemente para la profilaxis de la insuficiencia cardiaca y de los cuadros de encefalopatía, por ser estas dos complicaciones las más graves del padecimiento. Las nefritis agudas no han disminuído en frecuencia a pesar del uso excesivo de antibióticos en el tratamiento oportuno de las infecciones estreptocócicas; el objetivo fundamental de la terapéutica en la fase temprana sería el evitar las lesiones miocárdicas y cerebrales. Las primeras pueden presentarse aun en sujetos con tensión normal, acentuándose su peligro de instalación al observarse hipertensión; asímismo la amenaza de un cuadro de encefalopatía se debe tener siempre presente al aumentar la presión sanguínea en forma brusca y persistente a niveles elevados.

Hasta la fecha no se tiene una terapéutica específica definida, entendiéndose por esto la aplicación de una droga que llene estos requisitos: control de los factores que llevan a la insuficiencia cardiaca, reducción y control de los factores que predisponen a un cuadro encefálico y por último reducción del peligro de lesión parenquimatosa renal.

De los agentes actuales los derivados del veratrum son los más prometedores; por eso el autor ha empleado en esta serie de casos una mezcla de ésteres alcaloides denominada alka vervil (Veriloid, Riker Laboratory), que actúa sobre los tres sistemas mencionados. El veriloid puede darse por vía oral, intramuscular, o intravenosa. El autor empleó esta última a razón de 0.022 c.c. de la solución por kilo de peso como dosis inicial, seguida de otra dosis de 0.13 c.c. por kilo de peso sostenida hasta alcanzar un total de 22 c.c. de la solución por kilo, administrada a una velocidad de 5 gotas por cada 10 kilos de peso y por minuto.

Como la presión sanguínea de un niño sano o la de un niño con nefritis aguda varía fácilmente con diversos factores, cualquier procedimiento terapéutico que la disminuya debe valorarse con precaución. Igualmente puede reducirse la presión sanguínea de un niño con nefritis aguda en diversas formas a través de mecanismos hemodinámicos y fisiológicos diversos. Sin embargo, el análisis de los seis casos de este estudio seguidos durante los últimos dos años, sugiere que la terapéutica con veriloid es útil en el tratamiento de la fase hipertensiva ya que se observó un efecto hipotensor en cada uno de ellos. El autor acepta que aún no siendo el veriloid el agente ideal, su capacidad para reducir la resistencia periférica, bajar la presión sanguínea rápidamente, mantener la corriente sanguínea y el gasto cardiaco normales, hacen conveniente su experimentación más amplia en los niños.

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SYNDROME OF CONGENITAL HEMIHYPERTROPHY, SHORTNESS OF STATURE, AND ELEVATED URINARY GONADOTROPINS

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A DIFFERENCE between the two sides of the body occurs in mild degree in all individuals since true symmetry of the two halves does not exist. However, marked disproportion is not common, and less than 120 cases have been reported in the world literature. The nature and causation of this condition have never been satisfactorily explained although there have been many speculative theories as to the etiology. The purpose of this paper is to present two cases with a syndrome hitherto not described of hemihypertrophy, shortness of stature, and elevated levels of urinary gonadotropins.

CASE REPORTS

Case 1: P.J.H., a white girl, was first seen at the age of 5½ yr. because of a difference in the size of the 2 halves of the body.

She had been born at term after a normal delivery with no apparent abnormality but had weighed only 1818 gm. During a 6 mo. period of the pregnancy the mother had had several episodes of right upper quadrant pain and vomiting, and a diagnosis of "gall bladder disease" had been made. During the first years of life the patient was seen by physicians at routine intervals and considered to be doing satisfactorily, although she continued to be small. At 1 yr. she weighed 6.4 kg.

By the age of 2 yr., the parents had noted that the right side of her body was smaller than the left. The difference was already marked and did not become more noticeable during the next 3½ yr.

Four months prior to admission she was said to have been treated for a 2 mo. period with thyroid extract without any noteworthy effect on her growth or the asymmetry.

Past History: The child had always had a good appetite and had eaten an adequate diet. Solids were started prior to the age of 8 mo. Supplemental vitamins had been given during infancy.

She had sat without help at 9 mo.; stood at 10 mo.; said her first words at 1 yr.; and walked at 15½ mo. Her first tooth had erupted at the age of 13 mo. but dentition subsequently had seemed to be normal.

The mother was 27 yr. old, 155 cm. tall, the father, 29 yr. old, 160 cm. tall; a sister 2 yr. old was of normal height and symmetry. All were in good health, and the family history was entirely negative for any abnormality of growth or familial disease.

Review of systems was not contributory.

Physical Examination: She was a small, well-nourished, healthy child (Fig. 1). The entire right side of the body (including skull, chest, abdomen and extremities) was smaller than the left. Skin was of normal texture and moisture. It was clear except for a smooth-bordered pale 2 cm. café-au-lait spot which was present on the left lower abdominal wall. Face showed marked asymmetry with right side smaller than the left. Skull appeared large in relation to the face. No bruit was heard. Pupils were equal, reacted normally and the extraocular movements were normal. No abnormality of the fundi was seen. She had 20 deciduous teeth in good condition. Tonsils were enlarged but not acutely inflamed, and there was moderate anterior and posterior cervical adenopathy. Pulses were normal and equal on the 2 sides of the body.

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FIG. 1. P. J. H., aged 5½ yr. Note shortness of stature and hemihypertrophy.

The remainder of the physical examination was not remarkable.

Laboratory Data: Tuberculin and Wassermann tests were negative; Schick test was positive. Routine urinalysis was negative. Complete blood count was within normal limits. P.S.P.: 82% excretion in 2 hr. Serum calcium: 11.4 mg./100 cc. Serum phosphorus: 5.3 mg./100 cc. Total protein: 7.8 gm./100 cc. Hormonal serum iodine: 5.5 µg./100 cc. Total neutral 17-ketosteroids: 0.82 mg./24 hr. urine. Urinary gonadotropins: positive at 5 and negative at 80 mouse units. Two subsequent assays were positive at 5 and negative at 10 mouse units.

Roentgenograms of the skull and extremities were normal except for the difference in size of the bone on the 2 sides of the body. The bone age was normal.

Electroencephalogram was interpreted as being without normal limits for the age although a slight generalized paroxysmal dysrhythmia appeared during hyperventilation which was believed to have "no more than borderline significance."

At 6½ yr. of age, she was seen by Dr. Ralph Benson, the gynecologic consultant, who found that external genital development was normal. No abnormal mucosa or bleeding was present. An almost complete hymen prevented the taking of vaginal smears. On rectal examination the uterus was found to be normally positioned and approximately 2.5 cm. long. Both ovaries were felt and were firm

and mobile and about 2 cm. long. There was no detectable difference between the right and left. Dr. Benson's impression was that there was no palpable abnormality for a child of 5½ yr.

P.J.H. MEASUREMENTS

Birth wt.: 1818 gm.
Age: 5½ yr.
Wt.: 12.3 kg. (50 percentile for 2 yr.)
Ht.: 86.7 cm. (50 percentile for 2 yr.)
Head circ. 46 cm.
Chest circ. 49 cm.

	Right	Left
Arm, total length	32.5 cm.	36.5 cm.
Arm (acromion of clavicle to olecranon process)	14.0	16.0
Forearm (olecranon to styloid)	11.5	13.0
Leg (ant. sup. spine to heel)	43.0	47.0
Leg (tibial tubercle to heel)	19.0	20.0
Length of femur (by RG)	21.2	23.0
Length of tibia (by RG)	16.7	17.6

Peripheral Vascular Clinic Studies	Temperatures	
Upper Arm	30.2°C.	30.9°C.
Forearm	32.2	32.2
Mid palm	32.6	32.2
Upper leg	30	31.3
Anterior lower leg	30.7	31.5
Lower leg	30.3	30.6
Forefoot (sole)	29.9	31.4
Midsole of foot	29.6	30.8
Posterior part of foot	28.2	31.2

Case 2: B.W., a white boy, was first seen at the age of 6 yr. because of shortness of stature and a difference in the size of the 2 halves of the body.

He had been born at term but had weighed only 1730 gm., and had been 45.7 cm. tall. During the seventh month of the pregnancy the mother had been in an automobile accident. Although trauma was not considered to have been particularly severe and there had been no bleeding, she had had no further gain in weight from that time until the delivery of the child. Asymmetry between the 2 sides of the body had been noted immediately after birth, and the head had appeared large.

At the age of 3 wk. he had "gastroenteritis" with diarrhea and dehydration and his weight dropped to 1045 gm. Recovery was slow and the parents state that he has remained thin since that time. Appetite was poor during infancy, he vomited frequently, and he could eat only small amounts of food at any one time.

The parents reported that even though he had always been short, his growth had been at a constant, though slow rate. At the age of 3 yr. he had begun to have repeated attacks of tonsillitis and otitis media and had had some impairment of hearing since then.

He was said to have had various forms of therapy without any appreciable improvement resulting in his rate of growth or weight gain or in diminishing the difference in size of the 2 sides of the body. Treatment had included several months of thyroid extract at the age of 1 yr., "pituitary shots" (2 injections/wk. for a 2 mo. period when he was 3 yr. old), injections of "vitamin concentrate," and combined oral therapy with thyroid and pituitary extract and vitamin B_{12} between the ages of 4½ and 5 yr.

Past History: Diet had always been adequate with supplemental vitamins throughout. One peculiarity in his eating was that he had never been able to swallow particles of meat, although other solid foods were eaten without difficulty.

Development had been entirely normal. His first tooth had erupted at the age of 9 mo., and he had 5 teeth at 1 yr.

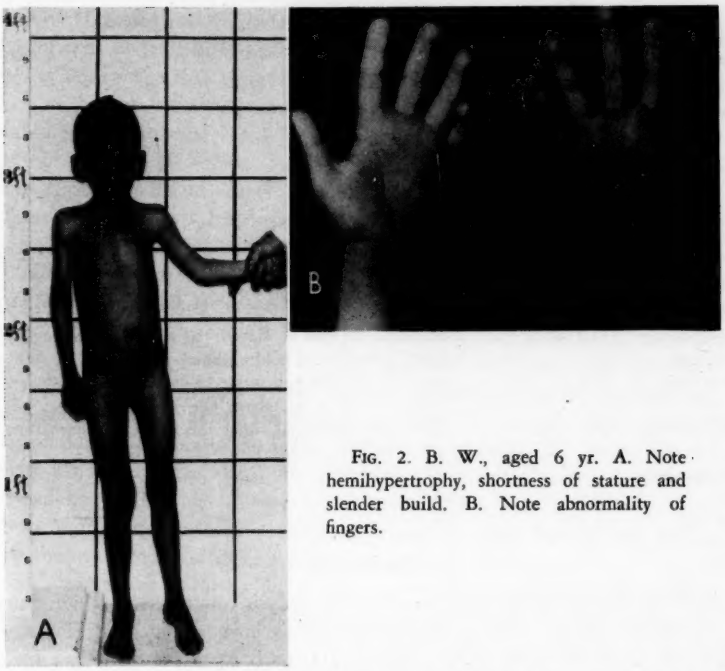

FIG. 2. B. W., aged 6 yr. A. Note hemihypertrophy, shortness of stature and slender build. B. Note abnormality of fingers.

The mother was living and well. The father was also in good health. He had a 6 × 8 cm. brown, pigmented hairy nevus on his arm. A sister, aged 2 yr., was of normal height and entirely well. The maternal grandmother had had a hemangioma of the chest. No growth disturbances in any members of family.

Review of systems was not contributory.

Physical Examination: He was an extremely small, thin boy with apparently normal intelligence. The entire left side of the body (including skull, chest, abdomen and extremities) was smaller than the right. Skin was of normal texture and moisture, and no pigmented areas or hemangiomas were present. Skin was tightly drawn over the face. Skull was of normal contour and no bruit was heard over it. Pupils were equal, reacted normally, and the extraocular movements were normal. He had 20 deciduous teeth. Tonsils were hypertrophied and slightly injected, and there was marked anterior cervical adenopathy. Heart, lungs and abdomen were not remarkable. Penis was of normal size. Testes were descended, and, although they were small, they were considered to be within physiologic limits. Pulsations were normal in all peripheral vessels. Blood pressure 104/50 mm.Hg (Fig. 2).

Laboratory Data: Tuberculin test was negative. Routine urinalysis negative. Complete blood count was within normal limits. Serum calcium: 10.2 mg./100 cc. Serum sodium: 132 mEq./l. Serum potassium: 4.2 mEq./l. Serum chloride: 98 mEq./l. Eosinophil response to the subcutaneous injection of epinephrin: before injection, 50 eosinophils/cmm. Four hours after injection, 6 eosinophils/cmm. Thorn test: before injection of ACTH: 25 eosinophils/cmm. Four hours after injection, 3 eosinophils/cmm. Serum protein-bound iodine: 7.1 gamma/100 cc. Uptake studies of radioactive I^{131} before and after the administration of thyroid-stimulating hormone were normal. Urinary 17-ketosteroids, 0.5 mg./24 hr. sample. Urinary gonadotropins: positive at 5 and negative at 10 mouse units. A subsequent assay was slightly positive at 5 and negative at 10 mouse units, while a third determination was negative at 5 units.

Roentgenograms of skull, esophagus, chest, abdomen and extremities were normal except for the difference in size of the bones on the 2 sides of the body. Bone age was normal but was different on the 2 sides of the body, being somewhat retarded on the smaller side.

B.W. MEASUREMENTS

Ht. at birth: 45.7 cm.
Wt. at birth: 1727 gm.

	Right	Left
Humerus	5.9 cm.	5.3 cm.
Ulna	5.6	5.2
Radius	5.0	4.7
Femur	8.6	7.9

At age 6 yr.
Ht.: 107 cm. (50 percentile for 4½ yr.)
Wt.: 12.5 kg. (50 percentile for 2 yr.)
Head circ. 50 cm.
Chest circ. 50 cm.

Length of arm	44.2 cm.	41.2 cm.	(End of clavicle to tip of index finger)
Forearm circ.	13.1	11.4	(4 cm. below elbow)
Length of entire leg.	54.0	50.0	(ant. sup. spine to medial malleolus)
Thigh circ.	25.2	22.5	(10 cm. above knee)
Length of foreleg	24.0	22.0	(Internal tibial tuberosity to internal malleolus of ankle)
Circ. of leg above knee	19.5	17.0	
Circ. of calf	17.5	16.5	

Discussion

Moderate asymmetry of the two halves of the body is common and is not considered to be significant, though marked hemihypertrophy is infrequently seen. However, it is probable that even the more severe varieties are much more common than the scarce number of reported cases would indicate. Total hemihypertrophy has been designated by various authors under the following names: "congenital hypertrophy,"[1] "unilateral hypertrophy,"[2] "true total hemihypertrophy,"[3] "hemigigantism,"[4] "partial gigantism,"[5] "hemimacrosomia,"[6] and "hemihypertrophy totalis."[7] In their excellent review of the subject, Ward and Lerner[8] have pointed out that an adequate evaluation of the cases reported is almost impossible because of the incompleteness of protocols and the lack of a uniform descriptive terminology.

Numerous etiologies have been suggested in an attempt to explain the origin of congenital total hemihypertrophy. Vascular lesions,[3,9,10] arteriovenous aneurysms, nevi, telangiectasis, lesions of the brain,[3,11] endocrine factors,[3,12] embryonic defects of the vegetative nervous system,[3] congenital syphilis,[3] abnormalities of the lymphatic system,[3,9,13] mechanical influences,[3] heredity, and embryonic variants (incomplete twinning),[9,14] have all been incriminated. None of the autopsied cases of hemihypertrophy have shown any lesions of the central nervous system, and RGs of the pituitary fossa[10,15,16] and postmortem examination of the pituitary gland[13,17] have failed to demonstrate any abnormalities.

Riedl[18] recently has reported the case of a boy with hemihypertrophy who had evidences of the adrenogenital syndrome as a result of an adrenocortical tumor and in whom an embryoma (Wilms' tumor) of the kidney subsequently developed, while Haridas and Gek[19] have reported the association of the adrenogenital syndrome and right segmental hypertrophy. Still other instances of hemihypertrophy with adrenal pathology are the cases of Hutchinson[20] who first reported the two in an infant 4 months of age with left-sided hemihypertrophy and a left adrenal gland three times larger than the

right, and of Harwood and O'Flynn[21] who described a boy with right-sided hemihypertrophy associated with virilism and a large right-sided adrenocortical tumor. The hypothesis has been made that either the tumor was part of the hemihypertrophy or that the tumor might have caused the hemihypertrophy "as an example of a predominantly unilateral effect of hormones secreted in the circulating blood by the cortical cells," but it would not explain the findings in Riedl's case where the hemihypertrophy occurred on the side opposite to the adrenocortical tumor.

Shortness of stature has been observed in relatively few of the reported cases of hemihypertrophy, and has not been consistently associated with any endocrine disturbance. In both of the patients reported here, the dwarfing and the asymmetry, which involved one entire half of the body, apparently had been present since birth.

Although one of these patients was said to have been born at term and the other was "10 days late" they had weighed only 1727 gm. and 1818 gm., respectively. In the former case, the mother's pregnancy had been complicated by the fact that she had been in an automobile accident during the beginning of the last trimester, and although there had been no definite trauma to the pelvic area and no bleeding, the mother did not gain any weight during the remainder of the pregnancy. During her pregnancy the mother of the girl had had gallbladder disease for several months. It is a matter of conjecture whether such unrelated disturbances during pregnancy could have played any part in producing the syndrome manifested by these two children.

Both had been short at birth, but it was reported that they had been growing at a slow but steady rate. The boy had seemed to be unusually thin at birth (weight 1.7 kg.; height 46 cm.) and disproportion of weight and height had continued to the present time (weight 12.4 kg.; height 105 cm.). His diet had been adequate, but he had had repeated episodes of tonsillitis, otitis media and cervical adenitis, and this might have played an important part in his failure to gain weight. No marked disproportion of height and weight were noted in the girl with this syndrome.

Investigative work-up in both was negative for any evidence of thyroid deficiency, bone disturbance, nutritional or metabolic disorder or disease of the circulatory system. The children had been tried on courses of thyroid extract with no apparent acceleration of their rate of growth or gain in weight. Testosterone by injection had been given to the girl, and it too had not produced any dramatic improvement.

Elevated gonadotropins for the age were found in both cases. By the method used in this laboratory, levels of gonadotropins in normal women during the reproductive period of life are greater than 5 mouse units and less than 80 mouse units. Normal children under 7 years of age never were found to have even as much as 1.25 mouse units in a 24 hour specimen of urine. On two occasions, five months apart, the girl was found to have an increased amount of urinary gonadotropins (positive at 5 mouse units), while the male patient had increased levels (more than 5 units) on one occasion, a "slightly positive" assay at 5 mouse units on another occasion and a negative assay for five mouse units on a third occasion. Variations in urinary gonadotropins occur in other conditions (i.e., ovarian agenesis) in childhood where levels are unusually high,[22, 23] but the authors have been unable to find a satisfactory explanation for these variations either in the syndrome being described or in ovarian agenesis.

The authors have wondered whether this condition might be a variant of ovarian agenesis (or the counterpart in the male) where shortness of stature, congenital abnormalities and elevated levels of urinary gonadotropins all may be part of the clinical

picture. However, the absence of the more common congenital defects of that syndrome (webbing of the neck, cubitus valgus, coarctation of the aorta, edema of the feet at birth, etc.) and the presence of apparently normal uterus and tubes on rectal examination of the female, and normal testes by palpation in the male made the diagnosis unlikely. The syndrome herein described and the syndrome of ovarian agenesis may be related conditions. One of the cases reported in the literature as "Malformational Syndrome Suggesting Ovarian Agenesis in Preadolescence" had shortness of stature, definite facial asymmetry, inward curving of both fifth fingers and "skin moles." In addition, she had sexual infantilism, congenital lymphedema, webbing of the neck, "shield-like" chest, cubitus valgus, osteoporosis, "infantile" nipples, and a congenital anomaly of the cardiovascular system.[24]

Studies of skin temperatures were carried out on one patient (the girl), and it is of interest that although hypertrophy involved the entire left side of the body, differences in temperature were much less marked in the arms than in the legs.

Ward and Lerner found associated abnormalities in 50% of the cases. These included abnormal nail growth,[2] premature eruption of teeth,[2] excessive secretion of sebaceous and sweat glands, [2, 25] thickening of the hair on the involved side,[9, 17, 25, 26] telangiectasia,[15] early appearance of varicose veins,[15] clubbed feet,[2] hypospadias,[16] cryptorchidism,[16] congenital heart disease,[16] polydactylism,[16] nevi,[2, 14, 16, 27] supernumerary nipples,[28] syndactylism,[9] pigmentation of skin,[1] enlargement of the tonsil[15] and hypertrophy of one of the paired organs on the involved side.[19]

The microscopic picture reveals true hypertrophy in all the systems. There is an overgrowth of the media and intima of the blood vessels[2, 29] and the muscle bundles are larger than normal.[30] The bones also show overgrowth.[25, 31–33] Hypertrophy of the interstitial connective tissue of the peripheral nerves is likewise described.[2] A café-au-lait area of the anterior abdominal wall was noted on the girl and neurofibromatosis with involvement of the hypothalamic or pituitary region must be considered as a possible cause of the disturbance. However, no other manifestation of neurofibromatosis was noted in this patient, and no evidence of the disease was found in the male with the same clinical syndrome as the girl.

Summary

Two cases of a syndrome of hemihypertrophy, shortness of stature, and elevated levels of urinary gonadotropins are reported. One of the children was a male, the other a female.

The hemihypertrophy and shortness of stature had been present since birth and the elevated gonadotropins were found at 5½ and 6 years, respectively.

The possible relationship to other conditions in childhood including those which also have increased gonadotropins is discussed.

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SPANISH ABSTRACT

Síndrome de Hemihipertrofia Congénita, Corta Estatura y Elevación de las Gonadotropinas Urinarias

Todos los individuos presentan diferencia de tamaño en los dos lados del cuerpo pues la simetría verdadera de las dos mitades no existe; sin embargo, la desproporción acentuada es muy rara, habiéndose reportado en la literatura mundial menos de 120 casos. Las causas y la naturaleza del síndrome nunca se han explicado satisfactoriamente. El presente trabajo se refiere a dos casos con

un cuadro no descrito hasta hoy integrado por hemihipertrofia, corta estatura y elevación de las cifras de las gonadotropinas urinarias.

El primero es el de una niña de raza blanca que habiendo nacido sin aparentes anormalidades pero con un peso de 1818 gramos, tuvo un desarrollo general normal, aunque siempre con estatura menor a la correspondiente; fue hasta la edad de dos años que los padres observaron mayor tamaño en la mitad izquierda del cuerpo; la asimetría incluía el cráneo, la cara, el tórax, el abdomen y las extremidades. Los datos de laboratorio fueron normales; las gonadotropinas urinarias se encontraron positivas a las 5 unidades rata y negativas a las 80 (dos análisis posteriores a su admisión revelaron positividad a las 5 unidades y negatividad a las 10 unidades rata); el estudio radiográfico de cráneo y extremidades no dieron datos patológicos excepto en cuanto al tamaño diferente en las dos mitades óseas; la edad ósea y el electroencefalograma se consideraron normales. El examen ginecológico reveló genitales externos, matriz y ovarios, con posición y tamaño adecuados a la edad de la niña.

El segundo caso se refiere a un niño también de raza blanca, llevado a la clínica a los 6 años de edad debido a su corta estatura asociada a asimetría corporal observadas desde el nacimiento. Su desarrollo fue lento, escaso, pero sostenido; padeció frecuentes ataques de amigdalitis; recibió tratamientos diversos a base de extracto tiroideo, extractos pituitarios, vitaminas, siempre sin ninguna manifestación de mejoría en su estado general. El examen físico mostró un niño delgado y pequeño, de inteligencia normal, con asimetría que incluía cráneo, cara, tórax, abdomen y extremidades, todas más pequeñas en su mitad izquierda. El pene y los testículos, aunque pequeños, se consideraron normales menos en relación a las gonadotropinas urinarias, positivas a las 5 unidades rata y negativas a las 10 (un examen posterior fue semejante y uno tercero negativo a las cinco unidades rata). El estudio radiográfico de cráneo, tórax, abdomen y extremidades reveló datos normales, fuera de la desproporción en tamaño de los huesos en ambos lados; la edad ósea fue normal aun cuando más retardada en el lado más corto.

La hemihipertrofia se ha designado de muchas maneras: hipertrofia congénita, hipertrofia unilateral, hemigigantismo, hemimacrosomia, etc. Su etiología se ha tratado de explicar en múltiples maneras: lesiones vasculares del cráneo, factores endócrinos, defectos embriológicos del sistema nervioso vegetativo, sífilis congénita, herencia, y recientemente asociándola al síndrome adrenogenital. La corta estatura no se ha observado con frecuencia en la hemihipertrofia pero sí en trastornos endócrinos diversos.

En los dos casos presentes fue negativa la investigación de trastornos endócrinos, óseos, nutricionales, metabólicos o circulatorios pero en ambos coincidieron niveles elevados de gonadotropinas urinarias; según el método de los autores los niños normales apenas si llegan a ser positivos a 1.25 unidades rata, con la orina de 24 horas. Las alteraciones en los niveles de las gonadotropinas urinarias se presentan, entre otros padecimientos en la infancia, en la agenesis ovárica, lo que hace pensar a los autores en probables relaciones de ambos síndromes.

En el 50% de los casos descritos en la literatura médica, se han encontrado anormalidades múltiples.

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ASSOCIATION OF ESCHERICHIA COLI SEROGROUP 0111 WITH TWO HOSPITAL OUTBREAKS OF EPIDEMIC DIARRHEA OF THE NEWBORN INFANT IN NEW YORK STATE DURING 1947

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INVESTIGATIONS into the etiology of epidemic diarrhea of the newborn infant carried out during the past decade have resulted in two important contributions. In 1943, Light and Hodes[1] isolated a filtrable agent which regularly produced diarrhea in calves in connection with four separate epidemics of this malady. This virus was not recovered from the stools of normal infants or normal calves. A more detailed account of this investigation was published in 1949.[2] In 1945, Bray[3] described the association of a single serologic type of Escherichia coli and epidemic diarrhea of the newborn infant. Previously, Adam[4] had reported the association of certain fermentation types (biotypes) of E. coli and infantile diarrhea, observations which were confirmed and extended by Goldschmidt.[5] Bray's contribution stimulated extensive studies[6–13] in Great Britain which established the facts that among more than 111 serogroups of E. coli two were present in large numbers of infants suffering from epidemic diarrhea and were encountered but rarely in healthy infants or infants suffering from other diseases. According to the classification of Kauffmann[14] these strains belong to serogroups 0111 and 055. The former has been referred to also as Bacterium neapolitanum, alpha or A type, and D433 and the latter as beta or B type. The findings of the British investigators were confirmed in other countries.[15–23] In the United States, reports on the association of epidemic and sporadic diarrheal disease and E. coli 0111 and 055 have appeared only since 1950.[24–26] In the present investigation fecal specimens which had been obtained from infants during two severe hospital outbreaks of epidemic diarrhea of the newborn infant in 1947 were studied in 1952 with regard to the presence of these serogroups of E. coli. This report summarizes the pertinent bacteriologic and epidemiologic data of the two outbreaks.

MATERIAL AND METHODS

In 1947, during 2 hospital outbreaks of epidemic diarrhea of the newborn infant, which occurred in 2 communities of New York State, specimens of intestinal content (feces or milk enema) were obtained. These specimens had been preserved at a temperature of −40° to −70° C. by Dr. Irving Gordon of the Division of Laboratories and Research, New York State Department of Health. In 1952 they were made available for bacteriologic study and shipped in dry ice; they were thawed in the refrigerator and immediately used for seeding of various culture media, namely, Endo agar, MacConkey agar, SS agar, desoxycholate citrate agar, and infusion broth. Following incubation of the solid culture media for 18 hr. at 37° C. individual colonies of E. coli were fished and identified on the basis of biochemical activities and antigenic structure. The broth cultures were seeded on the above differential and selective culture media and colonies of E. coli were studied in like fashion.

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The identification of the colonies as E. coli was based on the typical apperance on Endo and MacConkey agar, formation of acid and gas from glucose, lactose, sucrose, and other conventional test substances, production of indole, the methyl red and Voges-Proskauer reactions, and failure to grow in Koser's citrate solution. Agglutination tests were carried out at 50° C. with group-specific (0111, 055, and 026) E. coli (rabbit) antisera. Agglutination was noted grossly after incubation for 30 min. and 18 hr., respectively. Strains of E. coli of serogroups other than 0111 were kindly identified by Dr. William H. Ewing, Communicable Disease Center, Chamblee, Ga., who also confirmed the identification of one of the E. coli 0111 strains.

Results

Hospital Outbreak #1

This outbreak of epidemic diarrhea took place between July 29, 1947 and August 29, 1947 and involved 57 recognized cases. Eighteen of the patients succumbed (fatality rate of 32%). The outbreak apparently had its origin in an infant, aged 44 days, who was admitted to the Pediatric Section of the hospital on July 29, 1947. The exact mode of transmission to the infants who subsequently developed the disease could not be established with certainty, although several mechanisms had to be considered: the nursery in question was excessively large, housing 48 bassinets in a single room; common carriers were used to transport babies to mothers; babies were bathed on a common bath table; the thermometers for all infants were kept in a common container; nurses were assigned on alternate days to care for the infant with diarrheal disease on the Pediatrics Section and for the premature infants in the nursery; and the student nurse on night duty took care of both infected and premature babies. Clinically the disease did not differ from the description of epidemic diarrhea of the newborn infant. Stool specimens from two infants (R47-686 and R47-687) were available in 1952 for bacteriologic study. Both infants had developed the disease during the height of the epidemic. The infants had frequent loose, green stools and suffered from marked dehydration and weight loss; there was little evidence of febrile response. One of these patients succumbed.

Cultural examination in 1952 of the stool specimens from these two infants revealed the presence of E. coli and A. aerogenes. From one specimen 9 out of 10 individual colonies of E. coli and from the other 4 out of 4 such colonies were found to belong to serogroup 0111. The growth of E. coli serogroup 0111 was suppressed on SS and desoxycholate citrate agar in contrast to Endo and MacConkey agar, in accordance with similar observations reported previously.[25] The two strains of E. coli 0111 were specifically agglutinated by homologous but not by heterologous (055 and 026) antisera. Furthermore, the strains modified red blood cells, which became specifically agglutinable and lyzable by the homologous group-specific antiserum, according to the hemagglutination-hemolysis technic described recently.[27,28] The strains produced acid readily from 1% salicin, slowly from 1% sucrose, and rapidly from 5% sucrose and thus can be classified as biotype 1 according to Kauffmann.[14] It is evident, then, that E. coli 0111 of the identical biotype was present in both fecal specimens as the predominant E. coli organism.

Hospital Outbreak #2

The second outbreak took place from the end of 1946 to October 1947. For the entire period diarrheal disease of 4 or more days' duration occurred among 33 (2.9%) of 1118 full term infants and among 27 (31%) of 87 premature infants. The fatality rates were 6% for the former and 37% for the later. The existence of diarrheal disease in this particular hospital was brought to the attention of the Bureau of Epidemiology and Com-

municable Disease Control for the first time in June 1947. Source and mode of transmission of the disease could not be established with certainty. Following institution of an adequate control program,[29] no further serious cases developed.

Stool specimens were obtained on July 4 from five infants who had developed the disease during the last week of June of 1947. Specimens from two fatal cases were kept individually (R47-580, R47-584), those from one fatal and two nonfatal cases were pooled (R47-581, R47-582, R47-583). Bacteriologic examination in 1952 revealed the presence of E. coli 0111 in all specimens. Examination of individual colonies of E. coli present on Endo or MacConkey agar, which had been seeded directly with the specimens, showed that 31 out of 32 colonies belonged to this serogroup. Culturally and biochemically these colonies had the characteristics typical of E. coli and belonged to biotype 1 of Kauffmann. It may be concluded that, as in the previous outbreak, E. coli serogroup 0111 was present in all three specimens from the five infants and that it represented the predominant E. coli organism.

Presence of Various Serogroups of E. Coli in Healthy Infants and Infants with Mild Diarrheal Disease in a Hospital Nursery

Following the finding of the association of E. coli 0111 and two severe hospital outbreaks of epidemic diarrhea of the newborn infant it was deemed of interest to extend this observation to the study of additional specimens which were collected from healthy individuals and sporadic cases of mild diarrheal disease during a continuing program of supervision of a nursery in a hospital. None of the ill infants was seriously affected. The specimens which were collected on October 28, 1948, had been kept at −40° to

TABLE 1

PRESENCE OF VARIOUS SEROGROUPS OF E. COLI IN FECES OF HEALTHY INFANTS AND INFANTS WITH MILD DIARRHEAL DISEASE IN HOSPITAL NURSERY

		E. coli serogroups			
		020	021	033	071
Healthy infants	1	−	−	−	−
	2	−	−	−	−
	3	−	−	−	−
	4	−	−	−	−
	5	+	−	−	−
	6	+	−	−	−
	7	−	−	−	+
	8	−	+	+	−
Infants with mild diarrheal disease	1	−	−	−	−
	2	−	+	−	−
	3	−	−	+	−
	4	−	−	−	+
	5	−	−	+	+
	6	−	+	+	+

+ = E. coli present
− = E. coli absent

−70° C. until 1952, at which time a bacteriologic study was undertaken, as described above. Fourteen specimens were available; six had been obtained from infants with mild diarrhea and eight from healthy babies. The results of the bacteriologic study are summarized in table 1.

It is evident that E. coli 0111 or 055 was not found and that no one serogroup of E. coli was common to all diarrheal cases; nor was there a relationship between the presence of a given serogroup of E. coli and illness. It should be emphasized, however, that, as expected, infants in a nursery may share certain antigenic groups of E. coli.

Discussion

From the data presented in this communication it is evident that E. coli serogroup 0111 was present in all five fecal specimens obtained from seven infants who were suffering from severe diarrheal disease during two serious hospital outbreaks of epidemic diarrhea of the newborn infant. These outbreaks took place in two localities of New York State during 1947. Furthermore, it is important to point out that this particular serogroup of E. coli was present as the predominant coliform organism, inasmuch as 44 out of 46 colonies E. coli obtained from these specimens on primary plating were of this antigenic group. These observations indicate that in the United States, as in Great Britain, E. coli serogroup 0111 was associated with hospital outbreaks of epidemic diarrhea of the newborn infant as early as 1947.

The fact that E. coli serogroup 0111 could be isolated from fecal specimens which had been preserved at a temperature of − 40° to − 70° C. for five years suggests that similar investigations may be carried out in the future on material that has been preserved elsewhere for virus studies. It seems reasonable to anticipate that, if outbreaks of epidemic diarrhea should occur in a hospital where laboratory facilities are not available for the identification of the antigenic pattern of E. coli, specimens may be preserved in the frozen state for investigation elsewhere.

It must be stressed that the recovery of E. coli 0111 or of other serologic groups of this species, even as the predominant coliform organism, does not furnish proof of the etiologic role of this micro-organism. The concept of the pathogenic potentiality of E. coli serogroups 0111 and 055 (and possibly of other serogroups[30-33]) is based largely on epidemiologic data, to the effect that these serogroups of E. coli can be recovered in large numbers from infants suffering from epidemic diarrhea of the newborn infant and but rarely from healthy infants, children and adults. In addition, Ferguson and June,[34] June, Ferguson and Worfel,[35] Braun and Henckel,[36] Neter and Shumway,[26] Neter and Webb[37] have shown that the ingestion of, or exposure to, these serogroups of E. coli may be followed by mild gastrointestinal upset or severe gastroenteritis; in contrast, ingestion of "normal" strains of E. coli had no such effects. Furthermore, adult volunteers, following ingestion of large numbers of E. coli 055, developed group-specific E. coli agglutinins[35] and bacterial hemagglutinins[38]; the latter antibodies were demonstrated by means of the recently developed E. coli hemagglutination test.[27, 28]

Should eventually proof be forthcoming that a few of the numerous serogroups of E. coli are not only incidentally associated with, but actually responsible for, diarrheal disease of infants, then it will have been established that certain serogroups have pathogenic potentialities not shared by others. This concept of the relationship between antigenic type and disease would be neither novel nor unique. Attention may be called to the facts that pneumococcus type 1 (prior to the days of modern antibiotic therapy) was relatively

more often encountered in empyema than in lobar pneumonia, pneumococcus type 3 relatively more frequently in mastoiditis than in otitis media and, recently, that certain types of hemolytic streptococcus of group A are encountered relatively more often than other types in streptococcicosis complicated by acute glomerulonephritis.[39]

Since it appears that epidemic diarrhea of the newborn infant is not a mono-etiologic disease, it will be desirable in the future to carry out investigations into its etiology by studying suitable specimens for the presence of recognized, enteric pathogens, such as salmonellae, for viruses, such as the one described by Light and Hodes,[1,2] and for certain serogroups of E. coli, such as the one which forms the basis of the present report.

Finally, if, in the search for an animal virus, attempts are being made to reproduce the disease in suitable subjects by means of filtrates of fecal specimens, one should consider the possibility, however remote, that a filtrable agent active against bacteria may conceivably be responsible for the resulting illness. This interesting possibility arises from the observations[40–43] that bacteriophage or a similar filtrable agent may render nonvirulent (nontoxigenic) strains of Corynebacterium diphtheriae virulent (toxigenic) or transduce to certain micro-organisms many different traits. Were diarrhea to develop in such an individual following the ingestion of the filtrate, the resulting illness could be ascribed inaccurately to the activity of an animal virus rather than to that of the bacterial filtrable agent.

Summary

Escherichia coli serogroup 0111 was isolated in 1952 as the predominant coliform organism from 5 fecal specimens obtained from 7 infants who were suffering from epidemic diarrhea of the newborn infant during two serious hospital outbreaks of this disease in 1947. The specimens had been preserved at a temperature of − 40° to − 70° C. for five years. The association of certain serogroups of E. coli and epidemic diarrhea of the newborn infant is discussed.

Acknowledgments

The authors wish to express their appreciation to Dr. Irving Gordon of the Division of Laboratories and Research, New York State Department of Health, for making available the specimens from the patients and to Dr. William H. Ewing, Communicable Disease Center, Chamblee, Ga., for the determination of the serogroup of many of the E. coli strains.

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SPANISH ABSTRACT

Coincidencia de la Escherichia Coli 0111 con dos Brotes Hospitalarios de Diarrea Epidémica del Recién Nacido en la Ciudad de Nueva York durante 1947

Las investigaciones en la etiología de la diarrea epidémica del recién nacido en los últimos años han dado dos contribuciones importantes: la posible relación con un virus filtrable y con las Escherichia Coli clasificadas como 0111 y 055. Este artículo trata de la posible relación de la Escherichia Coli 0111 con dos brotes severos hospitalarios de diarrea epidémica del recién nacido que se basa en datos bacteriológicos y epidemiológicos sugestivos.

Se obtuvieron muestras de contenidos intestinal durante 1947 de varios niños de cada uno de los brotes señalados y se conservaron a temperaturas de —40° a —70° Centígrados; en 1952 los estudios bacteriológicos identificaron las colonias como de Escherichia Coli perteneciente al grupo 0111.

El primer brote epidémico se presentó de julio 29 a agosto 29 de 1947, comprendiendo 57 casos de los que 18 fallecieron (mortalidad de 31.6%). El brote se inició aparentemente en un niño de 44 días de edad; la forma de transmisión a los demás no pudo establecerse con seguridad aunque se consideraron varios mecanismos. El cuadro clínico se manifestó por evacuaciones frecuentes, aguadas, verdes, que produjeron deshidratación acentuada, pérdida de peso y respuesta febril en los niños. El organismo hallado se identificó como Escherichia Coli 0111.

El segundo brote se extendió desde fines de 1946 a octubre de 1947 y comprendió 33 (2.9%) de 1118 niños nacidos a término y 27 (31%) de 87 prematuros; la mortalidad fué de 6% para los primeros y 37% para los segundos. No se localizaron ni la fuente de contagio ni la forma de transmisión de la enfermedad. La Escherichia Coli 0111 se encontró en las materias fecales de los niños estudiados como el grupo coliforme predominante.

Este hallazgo de la Escherichia Coli 0111 y su asociación a dos brotes epidémicos hospitalarios obligaron a hacer un estudio en individuos sanos y casos esporádicos de diarrea ligera en un programa de supervisión en la cunera de otro hospital; no se encontraron en ellos ni Escherichia Coli 0111 ni 055.

De los datos obtenidos es evidente que la Escherichia Coli del grupo 0111 se asoció a los casos estudiados de ambos brotes epidémicos de diarrea. Este hallazgo no significa una prueba definitiva de la posible etiología de estos gérmenes; el concepto de su potencialidad patogénica se basa en datos epidemiológicos según estudios de numerosos autores, tanto de observación como experimentales. Si estudios posteriores demostraran más adelante que algunos de los grupos serológicos de Escherichia Coli no solamente se asocian sino son responsables de cuadros diarreicos en los niños, se habrá establecido que algunos coliformes poseen poder patogéno y otros no. Como parece ser que la diarrea epidémica del recién nacido no es un padecimiento de etiología única, ésta debe investigarse buscando diversos organismos.

219 Bryant Street

CHRONIC FAMILIAL NONSPHEROCYTIC HEMOLYTIC ANEMIA

By EARLE L. LIPTON, M.D., HERBERT J. GROSSMAN, M.D., AND JULIUS B. RICHMOND, M.D.
Chicago

RECENT studies in hematology have more clearly defined the obscure diseases comprising the hemolytic syndromes. Despite new technics and careful case studies there are still a number of disorders involving intrinsic cellular defects which cannot be specifically classified. Many have been described as familial "nonspherocytic hemolytic" anemias. The two sisters described in this report are of interest because of the difficulty in the initial confirmation of a hemolytic mechanism. The detailed clinical hematologic findings and their comparison with similar cases in the literature are presented.

CASE REPORTS

Re. was the first child of a 19 yr. old primipara. Birth weight was 2.3 kg. She was "slow in breathing" and therefore was placed in an incubator. There was some pallor on the third day of life and a RBC count of 2.9 million/cmm. was noted. No therapy was instituted. The infant was discharged 5 days later and subsequent administration of liver, iron and folic acid was without effect.

Patient's weight gain was excellent; the birth weight was doubled by 3 mo. At that time the patient received a transfusion, the first of what ultimately added up to more than 70. When she was 4 mo. of age, the liver and spleen were first noted to be enlarged.

At 23 mo. of age, Re. was referred to the University of Illinois Research and Educational Hospital for re-evaluation and therapy. Physical examination revealed an attractive, pale, blond-haired child with moderate splenohepatomegaly, cardiomegaly, shotty lymphadenopathy, an upper respiratory infection, and a mild otitis media. Her general appearance, physical activity and appetite did not seem to reflect the laboratory and physical findings (Fig. 1B).

The major findings were a slightly elevated serum bilirubin, but normal reticulocyte counts, sedimentation rates, liver function tests, and random urine specimens for urobilinogen. There was a normocytic, normochromic anemia. Bone marrow demonstrated moderate normoblastic activity. Heart was diffusely enlarged upon roentgenographic examination. In the course of the study the parents removed the child from the hospital. The tentative conclusion reached at that time was: "Anemia due to maturation arrest of the bone marrow at the normoblastic stage, congenital."

The child was again seen in the outpatient department at 4 and 5 yr. of age. For the first time the skin was noted to be pale lemon yellow in color. Spleen was palpable 6 cm. below the costal margin in the anterior axillary line; liver was 5 cm. inferior to the right costal margin at the midclavicular line. She was developmentally normal except for the persistently small head circumference.

At 5½ yr. of age, Re. was admitted, along with her younger sister, to the hospital for further studies which are reported below. Examination of the former revealed essentially the same physical findings as before. It was decided that the children manifested a nonspherocytic hemolytic anemia and splenectomy was performed on Re. A slightly enlarged but otherwise normal liver and a normal gall bladder were observed and palpated at surgery. A small accessory spleen was also removed.

Spleen weighed 330 gm. and measured 14 × 9 × 5 cm. The capsule was dark, red-brown and smooth. The cut surface showed numerous pinpoint white Malpighian bodies. The rest of the parenchyma was dark red with a granulated appearance.

Microscopic studies showed relatively large but widely dispersed lymphoid follicles. The red

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From the Department of Pediatrics, University of Illinois College of Medicine, Chicago.
(Received for publication March 20, 1953.)

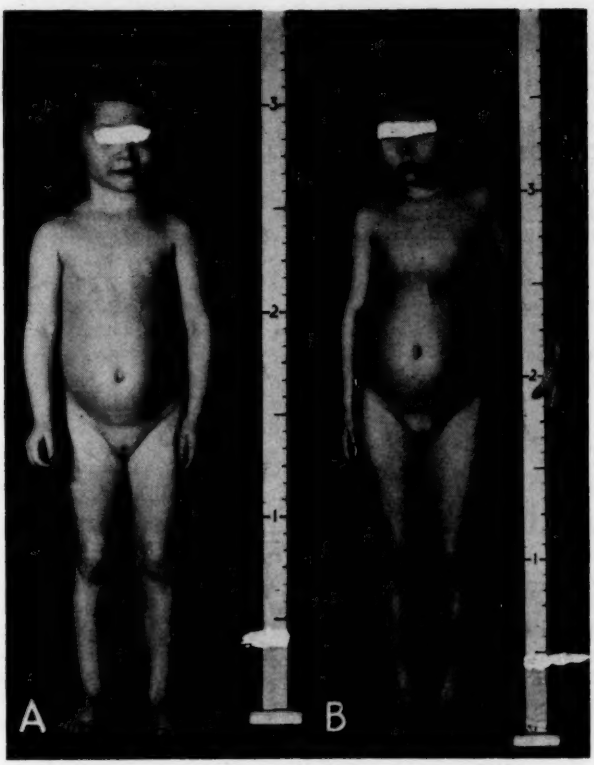

FIG. 1. A. Gr. at age 3 yr., 4 mo. B. Re., at age 5 yr., 10 mo. Note good growth, suggestive prominent cheek bones. Splenectomy was performed on latter 2 mo. prior to picture.

pulp was abundant, with rather widely separated trabeculae. A considerable number of erythrocytes and their precursors were present in the pulp spaces with few in the sinusoids. Diffuse extramedullary hematopoiesis was noted which consisted primarily of erythroid elements. The small accessory spleen 1 × 1 × 1 cm. showed similar findings. Special stains demonstrated very little iron in either spleen.

The postoperative course was uneventful, and the child has done remarkably well in the 16 mo. follow-up period. The stabilization of the erythrocyte count, hemoglobin and hematocrit are indicated in chart 1. Her last transfusion to the date of writing consisted of 100 cc. on the day of surgery. She had previously required transfusions every 2 to 4 wk.

After Re.'s birth the mother suffered a spontaneous abortion at 3 mo. and 1 yr. later the loss of a male infant at 5 wk. of age. The cause of death, which was sudden, could not be determined by the local physicians who performed the autopsy. Several previous blood counts had not revealed an anemia.

The following year Gr. was born after an uncomplicated pregnancy and labor. At birth she appeared "skinny, pale, and cyanotic" and was placed in an incubator for a short period, her birth weight being 2275 gm. The hemoglobin dropped from a level of 12.5 gm. on the day of birth to 10.5 gm. on the second day when 20 cc. of blood i.m. was given. A 60 cc. transfusion was given on the ninth day of life, and she was sent home. Transfusions were required at intervals of 3 mo. during the first year of life because of pallor, weakness and anorexia. An enlarged spleen was first noted at 10 mo. of age.

At 13 mo. of age, Gr. was admitted to the University of Illinois Research and Educational Hos-

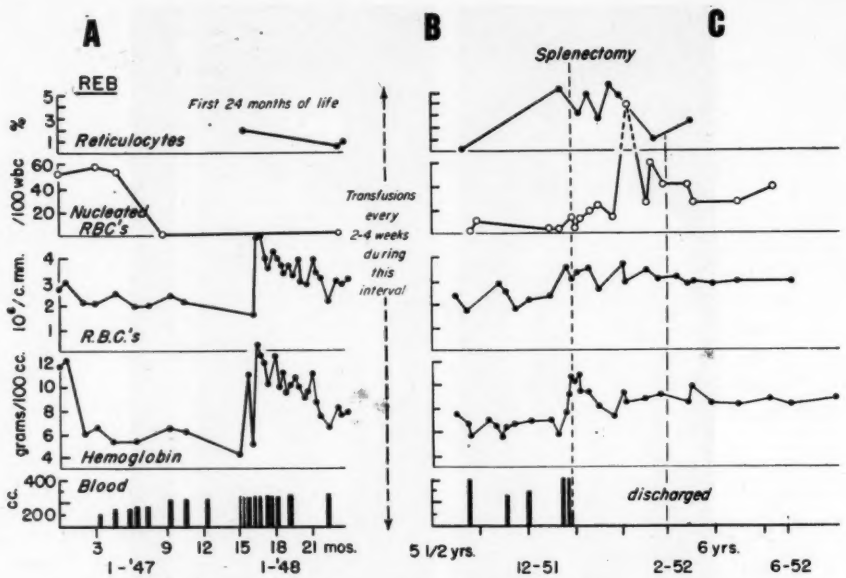

CHART 1. A First 2 yr. of life showing constant need for blood transfusions. Pre-transfusion hemoglobin and RBC levels were not often determined and blood given due to clinical indications. Severity of anemia is thus masked in this diagram. B. Four months of hospitalization. Note post-splenectomy response with normoblastosis, rise in hemoglobin and RBC levels and lack of any subsequent transfusion. C. Rather stable levels noted during outpatient observations after discharge from hospital.

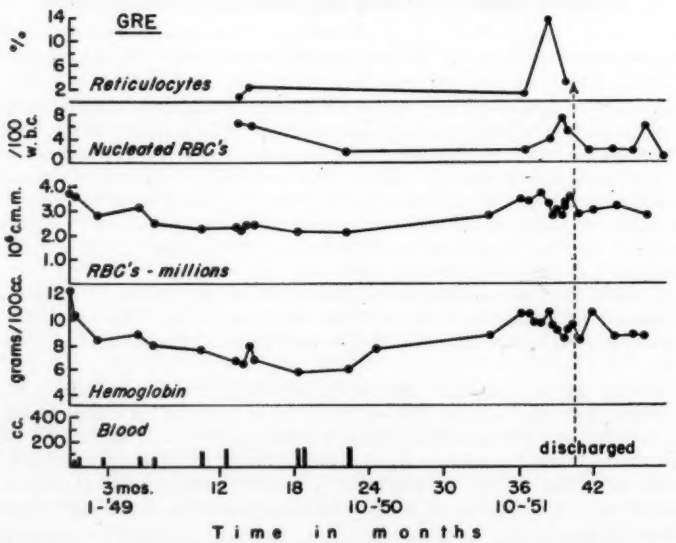

CHART 2. Rate of blood destruction was high during 1st 2 yr., necessitating transfusions. Subsequent course less severe and levels remain relatively stable without any therapy.

TABLE 1

Determinations (Normal values)	Re.		G.	Mother	Father
	Pre.	Postop.			
M C V (80–94 cu. microns)	94 (7×)*	96.8 (10×)	93.7 (11×)	89.5 (3×)	96 (2×)
M C H (27–32 micro-micro grams)	29.2 (36×)	29.6 (12×)	27.7 (24×)	27.5 (3×)	30.6 (2×)
MCHC (32–38%)	29.3% (7×)	31% (12×)	31.7% (12×)	31.9% (3×)	31% (2×)
Hypotonic saline frag.	Max—normal Min—increase		Max—normal Min—increase	Normal	Normal
Cell morphology	Aniso, poikilocytosis; budding, targets, nucleated		Same	Slightly hypochromic	Normal
Lysolecithin fragility	Decreased		Decreased	—	—
Mechanical fragility (up to 8%)	—	10.1% (2×)	11.5%	1.6%	3.4%
Alkali-resistant Hb (up to 1.7%)	2.26%	2.2%	1.17%	0.85%	0.83%
Reticulocytes and normoblasts	See figures		See figures	Normal	Normal
Serum bilirubin	Indirect is increased		Indirect is increased	0.3 mg./100 cc.	0.3 mg./100 cc.
Serum iron (.056–.170 mg./100 cc.)	—	0.225 mg./100 cc.	—	.086 mg./100 cc. (2×)	.082 mg./100 cc.
Fecal urobilinogen (24 hr.)	823 mg.	631 mg.	166 mg.	—	—
Hemolytic index	700	350	126	—	—
Urine urobilin	9.8 mg.	—	+.1 mg. (12-20-49)	—	—
Bone marrow	Erythroid hyperplasia		Erythroid hyperplasia	—	—
Blood type	B CdE/Cde		A CDe/cde MN	AB CDe/Cde	O CdE/cde

* Figures in parentheses indicate number of determinations employed in obtaining the average figure noted.

pital. Physical examination revealed pallor, an upper respiratory infection, a soft blowing apical systolic murmur and hepatosplenomegaly (each 4 cm. below the costal margin in the midclavicular line).

Diagnostic studies revealed similar findings to those of Re. except for slightly elevated reticulocyte counts (1 to 2%), elevated total serum bilirubin (1.0 mg./100 cc.) and 6 to 7% normoblasts in the peripheral smear. A 24 hr. quantitative urine urobilinogen was normal (less than 0.1 mg.). Gr. was discharged with the same diagnosis as that of her older sister, although there was much speculation regarding an hemolytic mechanism.

She, too, was seen in the outpatient department, but there were no changes other than her improved physical growth and decreased requirement for transfusions (chart 2).

At 3 yr. of age, Gr. was admitted for re-evaluation with her sister, and the findings were similar to those previously noted. Although she was in the 10% for height and weight in the first admission, she was in the 50% or greater for all measurements on readmission. No splenectomy was performed and she has been closely observed since discharge (Fig. 1A).

Two months later a male sibling was born whose chest RG and blood studies checked subsequently in this laboratory have been normal.

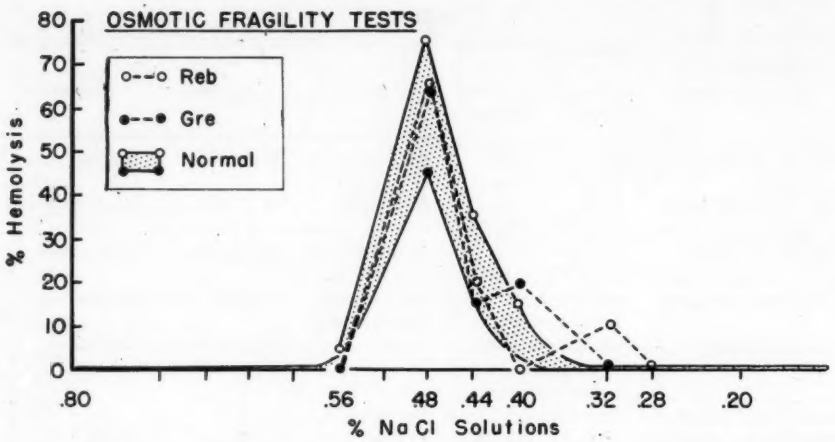

CHART 3. Osmotic fragility tests—charted in terms of hemolytic increments. Utilizing normal ranges discussed by Suess, Damashek et al.[4] there may be only slightly extended minimal hemolysis. Reticulocytes or other immature, thin cells may be responsible for this resistance to hypotonic solutions.

The father, 29 yr. of age, was born in Illinois. He has had occasional attacks of right upper quadrant and back pain with emesis, but the lack of recent symptomatology has delayed further investigation. There have been no abnormal physical findings.

The paternal grandfather died at the age of 67 yr. after an operation "for gallstones." The paternal grandmother, 66 yr. of age, is living and well but "anemic." This could not be proved. Their ancestry was Irish and German-Irish, respectively. Questionable reports of anemia in 2 of the father's 4 siblings also could not be documented.

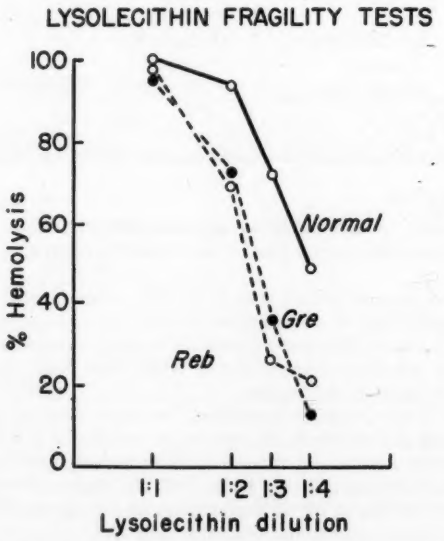

CHART 4. Lysolecithin fragility tests—demonstrate resistance to hemolysis in lysolecithin solutions by both patients' RBC's.

The mother, born in Arkansas, is 25 yr. of age and of English, Irish, Scotch and French descent. She has had no abnormal physical findings. Her father and 1 of her 5 siblings "may be slightly anemic."

Laboratory Findings

The following studies, in part illustrated in the accompanying table and charts, were done on both children simultaneously during a prolonged hospital stay of 4½ mo. The averages of all red blood cell indices are normal with the exception of a minimal decrease in the MCHC. Total serum bilirubin determinations in both children have been persistently elevated to levels of 0.9 to 1.6 mg./100 cc. due to an increase of the indirect fraction. Bleeding and coagulation times, clot retractions and capillary fragility tests have always been normal.

Urobilinogen excretion studies were done in both children (method of Watson). The decrease in excretion after splenectomy is shown in table 1.

Repeated immunologic studies for auto-agglutinins at 37° C. and Coomb's tests were negative. Very low titers at 4° were noted. No agglutinations were demonstrated in serum albumin against their own cells, other normal cells of their own type, O cells or papainized cells.

Bone marrow examinations have repeatedly shown mild to moderate hyperplasia with an excess of normoblasts. Hemosiderin pigment could not be demonstrated either in the urine or marrow employing ammonium polysulfide and prussian blue stain, respectively. Porphobilinogen was not found in the urine. Serum iron[1] in Re. was increased.

No sickling phenomenon was shown employing the sodium meta-bisulfite technic on repeated occasions. Rouleaux formation was always normal and wet and dry preparations of both children's bloods revealed moderate aniso and poikilocytosis with some budding and fragmentation. Occasional spherocytes, oval and pencil cells were noted and normoblasts were observed in almost all smears. However, Price-Jones curves revealed normal distributions both before and after splenectomy in Re.'s case. The average cell diameters were 7.36 and 7.64 μ, respectively. Morphologic studies of the white cells at no time demonstrated anything but an occasional shift to the left at the time of an infection. The leukocyte counts have correspondingly been elevated with infections and normoblastosis.

Mechanical, lysolecithin,[2] and osmotic fragility studies and alkali-resistant hemoglobin determinations[3] are summarized in table 1. (See charts 3 and 4.) Studies of the red blood cells' resistance to hypotonic saline solutions[4] after 24 hr. of sterile incubation revealed no particular deviations when compared to a normal control. Re.'s fragility studies showed no variations before and after splenectomy. An increased amount of alkali-resistant hemoglobin was found only in her blood.

Repeated NPN, total serum protein and A/G ratios, cholesterol and cholesterol esters, cephalin

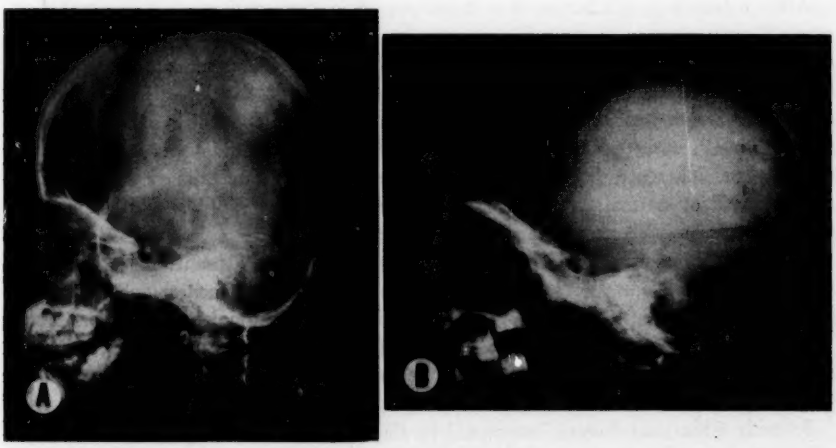

Fig. 2. A. Re.'s skull—note shortened A-P length and premature closure of coronal sutures. B. Gr.'s skull—note relative length and normal sutures. Both show thickening of diploic portions.

flocculation and thymol turbidity determinations have been normal. Electroencephalograms only showed tachycardia.

Roentgenograms revealed several interesting findings:

1. Both Re. and Gr. had a marked increase in the trabeculations of all cancellous bones with "punched out" areas and thin cortices.

2. Re.'s skull shape was brachy-turrecephalic with questionably increased digital markings and definite premature closure of the coronal sutures (Fig. 2).

3. A persistent generalized cardiac enlargement was always noted in Re.'s chest RG but has become much less marked since surgery. The younger sister's heart size was always normal but occasional patches of parenchymal density consistent with a clinically demonstrable pneumonia were present.

Studies of the blood of both parents revealed no definite abnormalities. (See table 1.) Serum iron determinations[1] were within the normal range.

Discussion

Proof of the existence of an active hemolytic mechanism rests basically upon the demonstration of a shortened life span of the red blood cells in the circulation. Life span studies could not be carried out with Gr.'s blood due to the rare A_1B type recipient who would be necessary. The older sister's circulation at the time contained too many donor erythrocytes which would nullify the results. The proof lay in the demonstration of a hyperactive marrow with reticulocytosis and normoblastosis, a persistent hyperbilirubinemia, and a markedly elevated excretion of fecal urobilinogen.

The one normal 24 hour urine urobilinogen determination in Gr. during the first admission was not sufficient to rule out an hemolytic process. The importance of fecal urobilinogen determinations and estimation of the hemolytic index is evident.[5,6] A recent report[7] cited the range of fecal urobilinogen determinations in normal children of all age groups. When the approximate hemolytic indices were calculated from the figures, it was found that almost all results were within the established normal range of 10-21 mg./100 gm. circulating hemoglobin. The few exceptions were all below 30 mg. The total problem of hemoglobin synthesis and its relation to the excretion of bile pigment has been adequately discussed elsewhere.[8]

After a hemolytic mechanism was demonstrated in these patients the presumably abnormal erythrocytes were studied in greater detail. It is obvious from the data presented that neither congenital spherocytosis nor sickle cell anemia can be considered. An acquired hemolytic anemia could not be demonstrated after repeated testing for abnormal agglutinins and hemolysins. It was recognized that studies to establish an immunologic mechanism are unsuccessful in some cases of acquired hemolytic anemia. The familial tendency and inherent cellular defects at any rate preclude such a primary diagnosis. Life span studies[9] of normal type O blood transfused into these children will be done to demonstrate a probably normal survival time in their circulation.

Thalassemia major is similar in some respects to these cases, but such a diagnosis is untenable because one almost invariably finds a markedly hypochromic and often a microcytic anemia. Furthermore, a large proportion of the hemoglobin is alkali resistant (type F).[10] Re. alone showed only a slight elevation. The marked fragmentation, stippling of the erythrocytes,[11,12] and immature leukocytes were also absent in these cases, as were the abnormalities in the blood of the parents.[13,14]

Recently Chini and Valeri[15] attempted to classify the various atypical Mediterranean syndromes and related a group of cases in which the hemolytic component was marked with frequent crises. Unfortunately, many of the differential tests were not reported to

better distinguish the specific cellular defects, and this makes comparison with our cases almost impossible.

Several recent reports in the American literature present well documented cases of familial nonspherocytic hemolytic anemia similar to these cases. Kaplan and Zuelzer[16] in 1950 described 3 of 6 siblings, a boy and 2 girls, who had a chronic hemolytic disease since infancy. The cells did not appear abnormal though their life spans were distinctly shortened. The fragility studies (mechanical and osmotic) were normal. In the boy an interesting finding was the premature closure of the coronal sutures.

The same authors later described an Italian-American family[17] in which 2 of 4 siblings died of anemia and icterus in the newborn period. Two subsequent female children survived after receiving frequent transfusions and seemed to respond to splenectomy by maintaining hemoglobin values of 6 to 8 gm. without transfusions. Hypotonic saline fragility studies showed some increased resistance of the cells but the mechanical fragilities were normal. Cell survival studies proved that an intrinsic cellular defect was present.

Crosby[18] described an adult with a marked hemolytic process but normal erythrocyte fragility. Splenectomy was unsuccessful, but siderocytosis (iron-staining particles in the erythrocytes) and porphobilinogen were found afterward. The present authors could demonstrate neither in these cases. In Crosby's family a hereditary bony dysplasia, brachyphalangia, was noted.

Debré in 1938[19] described brachycephaly and hand and jaw anomalies in hemolytic anemias. Unexplained premature synostoses were described. Re. has early roentgenographic evidence of premature synostosis of only the coronal sutures.

A case of nonspherocytic hemolytic anemia in which siderocytes were found was reported by Feinberg and Watson,[20] and others were reviewed by Dameshek.[5] This finding is probably not peculiar to one particular hemolytic syndrome; it may also be found in acquired types. Haden[21] described two families with atypical syndromes and basophilic stippling, but the report is lacking in details. No siderocytes have been noted in the present authors' studies.

Other cases which are suggestive of atypical hemolytic anemias unlike these were reported by Mills and Lucia,[22] Rundles and Falls,[23] Evans,[24] Young,[25] Stransky,[26] and Dacie et al.[27] It is difficult to compare many of these cases because technics for differentiating the specific defect of the erythrocytes were not available to the authors.

The heterozygous carriers of a hemolytic syndrome may have subtle and as yet undetectable abnormalities.[10] None could be demonstrated in the parents of these patients (table 1). Electrophoretic studies have not yet been performed. Other members of the family have not been cooperative, and there is only some historical evidence that other generations may have manifested a hemolytic disease.

The earlier diagnosis of an anemia due to a maturation arrest was considered because of only questionable evidence of hemolysis, and the early onset of anemia. This diagnosis was not fully accepted because of the maturity of the red cell precursors and the frequency of transfusions. Localized areas of hyperplasia in a generally hypofunctioning marrow had been the explanation for the occasional normoblasts and minimal reticulocytosis. The opposite has also been described: a hypoplastic marrow in cases of hemolytic anemia, thought to be due to marrow exhaustion or "marrow shutdown" in crises.[28]

It may be that more cases of so-called hypoplastic and aregenerative anemias will ultimately be shown to be on a hemolytic basis. Cathie[29] has described five nonfamilial cases of "erythrogenesis imperfecta" in which there were neonatal anemias, normoblastosis,

occasional abnormal bilirubin levels, and often normal or hyperplastic bone marrows. No fecal urobilinogen studies were reported, and one can seriously wonder whether at least some of these anemias involved a hemolytic mechanism.

Another recent report[30] cites two cases of hemolytic anemias originally thought to be due to a hypoplastic mechanism. In the Scandinavian literature is a case[31] of "hypoplastic anemia" characterized by bone marrow hyperplasia and a markedly increased serum iron. Kunz[32] reviewed the cases of Fanconi syndrome in the literature and noted a frequent hemolytic mechanism to account for the associated anemias. Smith[33] has already cited the problem of re-evaluating the "variety of blood disorders now included in the general category of the aplastic-hypoplastic type of anemia."

Splenectomy was performed on Re. on a purely empiric basis. During this brief post-operative period of 16 months, the rate of hemolysis has decreased to such an extent that the marrow can now better keep pace with the blood destruction. Gr. has required no transfusion for over two years. She may not be operated upon unless her rate of hemolysis increases and then only if her older sister continues with such an excellent response.

Recently, Young[34] documented the role of the spleen in removing intrinsically abnormal cells in at least one hereditary hemolytic syndrome, congenital spherocytosis. The red cells produced by Re.'s marrow are still abnormal, but a lower grade of destruction continues. It is conceivable that with noxious stimuli such as infections, or with time alone, she will return to her original rate of hemolysis.

Even if her course continues satisfactorily, however, this child runs a risk from generalized hemosiderosis and cholelithiasis. The risk is less than that of transfusion hepatitis or a so-called exogenous hemochromatosis due to repeated transfusions. Many recent articles survey areas of current and proposed investigations which may disclose the basic pathophysiology, and thus result in a more directed type of therapy in these patients with intrinsic disorders of the erythrocyte.[10, 35]

Summary

The authors have presented the problems in the diagnosis of an obscure anemia in two sisters which was apparently present at birth. The mechanism could not be established during the initial period of observation. Re-investigation revealed a nonspherocytic, familial, probably hereditary and possibly sex-linked hemolytic anemia.

These cases do not fit into any known specific category and are compared with other nonspherocytic hemolytic anemias recorded in the literature. It is suggested that other cases considered to be hypoplastic or aregenerative anemias be re-investigated to exclude the possibility of a hemolytic component.

Acknowledgment

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Addendum

Gr.'s spleen was removed at 57 months of age due to the findings of a rising serum bilirubin (1.7-3.0 mg./100 cc.), and increasing anemia, anorexia and recurrent infections. The fecal urobilinogen was 15 mg./24 hours one week after surgery but continued normoblastic hyperplasia in the marrow was found two weeks later.

Seven weeks postoperatively the following results were obtained: Hgb. 9.5 gm./100 cc.; RBC count 3.4 million/cmm.; hematocrit, 27.5%; total serum bilirubin, 0.69 mg./100 cc.; reticulocytes, 0.2%; and normal autohemolysis after incubation of defibrinated and clotted blood. Gr. is clinically improved despite the partially compensated hemolysis which persists.

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SPANISH ABSTRACT

Anemia Hemolítica Crónica Familiar no Esferocítica

A pesar de los avances recientes en la hematología que tienden a aclarar algunos puntos obscuros en los síndromes hematológicos, aún se encuentran padecimientos de esta naturaleza que engloban defectos celulares intrínsecos sin clasificación específica posible. Muchos de ellos han sido descritos como casos de anemia familiar hemolítica no esferocítica.

Tal es el problema de estas dos hermanas, descrito en el presente trabajo. Su interés radica en la dificultad inicial para confirmar el mecanismo hemolítico, aparentemente existente en ambas desde el nacimiento; fué necesario hacer un nuevo estudio hematológico para llegar a la conclusión de que ambas presentaban una anemia no esferocítica, familiar, probablemente hereditaria y unida al sexo. Estos casos no se adaptan a una clasificación específica hematológica; se hace un estudio comparativo con otros casos de anemia hemolítica no esferocítica citados en la literatura. Los autores, asímismo, sugieren que se reinvestiguen desde el punto de vista clínico-hematológico, otros casos considerados como anemias hipoplásticas y arregenerativas a fin de eliminar la posibilidad de que exista en ellas un componente hemolítico.

1819 West Polk Street

STUDIES OF THE IMMUNOLOGY OF THE NEWBORN INFANT

V. Effect of Dietary Protein on Antibody Production

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THE adequacy of protein in the diet is determined by the quantity and quality of the protein. It is a commonplace clinical observation that milk proteins supply a sufficient variety of amino acids to support growth in infancy. However, the optimum amount of protein for the growing infant is not known. This uncertainty is reflected in the wide range of protein content in the artificial milk formulas now offered for use.[1] These vary from a relatively low protein content of 1.5% in formulas that are designed to resemble human breast milk to formulas that contain almost three times that amount. The approach to this problem in the past has been to study the effect of these formulas on weight curves and nitrogen retentions. But the results leave unanswered the perennial question of maximal versus optimal nutrition.[2]

It was hoped that the use of a different approach to "optimal" might help resolve the problem. The authors have therefore studied the effect of diet on the ability of the infant to form antibodies. Two groups of infants were fed milk formulas of different composition, one with a protein level of 2.0%, providing 10% of the calories, and the other with almost twice that amount (3.6%) providing 20% of the calories. The formulas were fed *ad libitum*. Assuming an average daily intake of 100 calories/kg. body weight, the infants on the diet with the higher protein content received protein 5½ gm./kg. and the others received protein 3 gm./kg. The infants were immunized with a single injection of diphtheria toxoid and their antibody responses compared. The advantages of studying antibody formation in this manner have been previously described.[3] A superior antibody response in either group would suggest a better ability to resist infection.

PROCEDURE

Part I of this study[3] describes the manner of immunization and the methods of titration of antitoxin response. The artificial milk mixtures were prepared† from skimmed milk to which was added a fat mixture consisting of corn oil, coconut oil, olive oil, cocoa butter and butter fat. The calcium phosphorus ratio was adjusted to 1.3 by the addition of calcium gluconate; the pH was adjusted with citric acid and the Na:K ratio brought to 0.30 with sodium and potassium citrates. The caloric content of the 10% protein formula was raised with lactose, and ascorbic acid and fish liver oil concentrate were added to both milk mixtures. The completed mixtures were spray

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† The artificial milk mixtures were prepared by the M & R Laboratories through the courtesy of Mr. Dave Cox.

dried and packaged in cans. They were reconstituted with water before use. The 2 formulas were isocaloric but differed in composition as below:

	20% Protein Diet		10% Protein Diet	
	gm. %	% Distribution of Calories	gm. %	% Distribution of Calories
Protein	3.6	21.5	2.0	11.3
Fat	3.5	45.5	2.0	25.2
Carbohydrate	5.6	33.0	11.2	63.5
Ash	1.0		.5	
Calories/oz.		20.8		20.5

The study was conducted at the New York Foundling Hospital, an institution concerned primarily with the care of healthy children awaiting placement. Infants under 3 wk. of age were admitted to the study and assigned alternately to receive the 10% or 20% (by calories) protein formula. All infants received vitamin supplements in the form of a multivitamin preparation. No other foods were given as long as the infant was on the special milk formula. This regimen was maintained for at least 1 mo. and usually 2 or more mo. after immunization. Since the diet was begun on admission

TABLE 1

RELATION OF DIPHTHERIA ANTITOXIN PRODUCTION TO DIET

Age	Diet	Duration* of Diet (mo.)	Titres			
			2 wk.	1 mo.	2 mo.	3–4 mo.
Newborn						
1	10%	2	<.002	<.002	.006	.03
2	10%	1	<.002	<.006	.02	
3	20%	2½	<.002	<.002	.02	
4	10%	3½	<.002	<.002	.03	.05
5	20%	1	<.002	<.002		0.1
6	10%	2	<.002	<.002	.004	
7	20%	1	<.002	.02	0.1	
8	10%	1½	<.002	<.002		0.1
9	20%	3	<.002	<.002		.04
1 mo.						
1	10%	3	<.002	<.002	0.15	0.10
2	20%	2	<.002	.004	0.10	
3	20%	1	<.002	<.002	0.10	0.20
4	20%	2	<.002	<.002	.01	
5	20%	4	<.002	.01	0.10	0.10
6	10%	4	<.002	.03	0.15	
7	10%	4	<.002	.02	0.2	0.15
8	10%	3	<.002	.006	.01	
3 mo.						
		Pre† Post†				
1	20%	2 2½	<.002	.02	0.1	0.15
2	20%	3 2½	<.002	.02	0.1	
3	10%	5 3	<.002	<.002	0.2	0.25

* "Duration of Diet" refers to period maintained on diet after immunization. Diet was begun 1–3 wk. before immunization.

† "Pre" gives duration of diet prior to immunization.
"Post" gives duration of diet postimmunization.

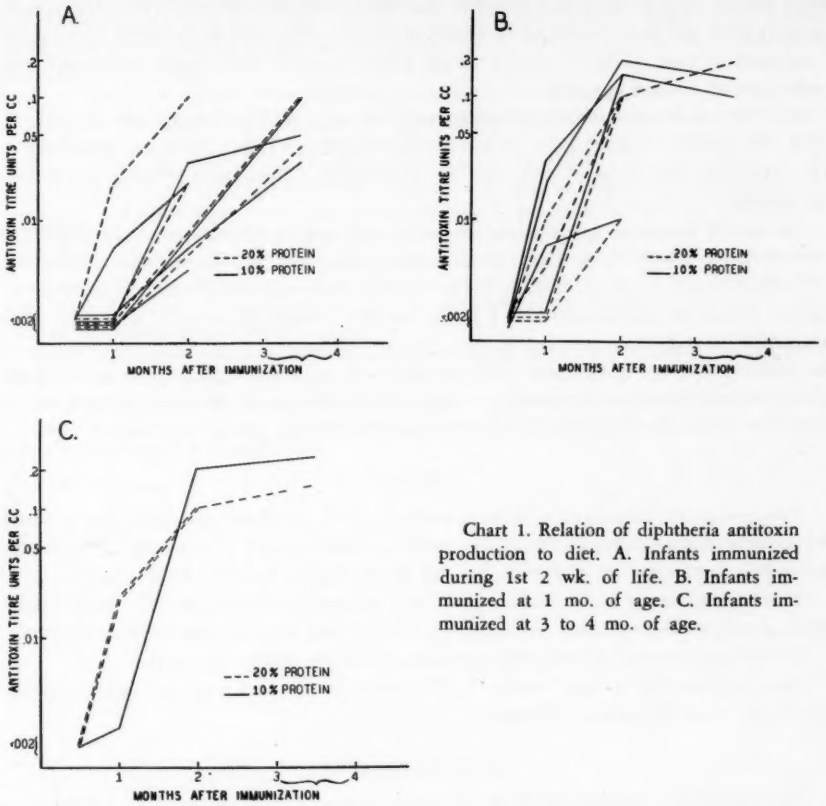

Chart 1. Relation of diphtheria antitoxin production to diet. A. Infants immunized during 1st 2 wk. of life. B. Infants immunized at 1 mo. of age. C. Infants immunized at 3 to 4 mo. of age.

to the hospital, the length of time the infant was on the diet prior to immunization varied with the age of immunization.

Infants were immunized at 1 of 3 ages: during the 1st 2 wk. of life (newborn), at 1 mo., or at 3 to 4 mo. of age. Some attempt was made to equalize the number of infants on each diet in each age group. Towards the end of the study, all infants were immunized at 1 mo. of age and diet assignments were made on a random basis.

A single injection of a potent diphtheria toxoid was given subcutaneously at the designated age as previously described, and the circulating antitoxin level was determined periodically thereafter. Infants were dropped from the study if they had circulating antitoxin prior to immunization,[4] or if they were discharged from the hospital less than 1 mo. after immunization preventing sufficiently prolonged control of the diet. In addition, an occasional infant had to be excluded because of intercurrent infection on some other problem that interfered with normal welfare and weight gain.

Results

The results are presented in table 1 and chart 1. There is no apparent difference in the antibody response between the infants who received the 10% protein formula and those on the 20% protein formula.

Discussion

Balch[5] has reviewed the literature on the effect of severe protein depletions on anti-

body formation and has added his own observations. In the study reported here, present authors have not been interested in severe depletion, but rather in the effect on antibody formation of two levels of protein intake which conform with those levels commonly prescribed in pediatric practice.

Of 151 infants admitted to the study, only 20 are considered satisfactory for this report, for reasons explained in the section on Procedure. This gives some indication of the difficulties presented by this type of investigation. Fortunately, certain conclusions are possible.

Infants of the same age and on the same diet vary in their response to diphtheria toxoid. Given a sufficiently large series, a minor difference of this response attributable to protein intake might be demonstrable. A sufficiently major difference in antibody response should be demonstrable in a small carefully controlled series. It is obvious from inspection of the accompanying figures that no difference in antitoxin production can be detected between the infants raised on the 10% protein diet and those receiving the 20% protein formula. Apparently, if antibody production is influenced by protein intakes, the relationship must be studied at intakes below 3 gm. protein/kg./day.

Summary

Two groups of 10 infants each were maintained on isocaloric milk formulas in which the protein content differed. One group received a milk formula containing 2.0% protein providing approximately protein 3 gm./kg. body weight; and the other group received a formula containing 3.6% protein providing approximately 5½ gm./kg. body weight. Both groups were immunized with diphtheria toxoid and the antitoxin response measured.

No difference in the antitoxin response between the two groups was seen.

This suggests that a high level of milk protein in the diet does not measurably improve the ability to produce antibodies.

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Spanish Abstract

Estudios Sobre la Inmunología del Recién Nacido

II. Efecto de las Proteínas de la Dieta en la Producción de Anticuerpos

La cantidad y la calidad de las proteínas en una dieta determinada fijan su papel en el desarrollo del niño; sin embargo, no se sabe aún cuál es la cantidad óptima de proteína que se requiere para

un desarrollo también óptimo. El enfoque sobre este problema se ha hecho a través del efecto que fórmulas variadas de leche tienen sobre las curvas de peso y la retención de nitrógeno en los niños. El presente trabajo procuró realizar un enfoque diferente, al estudiar el efecto de la dieta en la formación de anticuerpos.

A dos grupos de lactantes se les administraron fórmulas lácteas de composición diferente, en tal forma que siendo isocalóricas, uno de los grupos recibiera tres gramos de proteína por kilo de peso y otro 5 gramos y medio de proteína por kilo de peso. Todos los niños fueron inmunizados con una inyección de toxoide diftérico; posteriormente se compararon las respuestas en anticuerpos.

A los niños se les dió alternativamente la fórmula proteica correspondiente, suplementada con vitaminas; el régimen se mantuvo desde un mes previo a la inmunización hasta dos meses después. La inmunización se realizó en 3 fechas: durante las primeras dos primeras semanas de vida, al mes y a los tres o cuatro meses de edad, procurando equilibrar el número de lactantes con cada dieta, en cada uno de estos grupos. Al final, se estudió un grupo inmunizado solamente al mes de edad, asignándoles las dietas al azar. El toxoide diftérico se aplicó por vía subcutánea; la antitoxina circulante se determinó periódicamente.

Según los resultados obtenidos, los autores concluyen que no hay diferencia aparente en la respuesta de anticuerpos en los grupos de lactantes estudiados con las diferentes dietas y, por lo tanto, no tienen pruebas para admitir que la resistencia a la infección, considerada desde el punto de vista de la capacidad de los niños para producir anticuerpos activos, sea aumentada por una concentración mayor de proteínas en la fórmula láctea.

477 First Avenue

DIABETES INSIPIDUS IN INFANCY RESISTANT TO PITRESSIN

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AMONG the disturbances in water metabolism which resemble neurohypophyseal diabetes insipidus, there is a rare condition, present at birth, which is not responsive to administered posterior pituitary extract. Recent reports[1-3] have suggested that in certain cases of congenital diabetes insipidus the excessive urinary excretion may be due to an end-organ defect; a congenital anomaly of renal tubular function resulting in a kidney unable to respond to normal hormonal control.

The report of this patient is of interest because of the development of abnormal water balance early in life, the failure of recognition of this syndrome and its associated findings for many months, and an investigation of some aspects of this unusual congenital metabolic disturbance.

CASE REPORT

G.M., a 6½ mo. old Negro male (Fig. 1), was admitted to the hospital because of persistent fever, vomiting, dehydration, constipation and failure to gain weight.

The patient was born out of wedlock and the father's family history is not known. In the past 4 generations of the mother's family, there were only 3 boys and one of these was said to drink excessive amounts of water. He was born at full term following a normal pregnancy and labor. Birth weight was 2.3 kg. He appeared to be a normal newborn and went home with the mother on the third day of life. During the first month, however, he cried excessively, was irritable, vomited repeatedly and seemed to urinate continuously. The stools were unusually dry and the mother remarked that he always felt warm. At the age of 2½ mo. he was taken back to the hospital where he was born because of persistent vomiting and failure to gain weight.

On admission to that hospital, he weighed 2.7 kg. During the 4 mo. of his hospitalization, his fever ranged from 37.2° to 40.0° C. daily and did not respond to many of the commonly employed agents such as sulfadiazine, penicillin, sulfamethazine, sulfamerazine, streptomycin, aureomycin and terramycin. He vomited a variety of formulae and required frequent intravenous infusions because of persistent dehydration. There was moderate anemia and normal white and differential blood counts. Urine examinations were reported as normal. Other investigations, including blood cultures and agglutinations, intravenous and retrograde pyelograms, and roentgen studies of the skull, long bones, chest and gastrointestinal tract provided no explanation for the persistence of fever and vomiting. Brain abscess was suspected because of the nature of the fever and vomiting but there were no abnormal neurologic findings. Fundi appeared normal, and repeated spinal and subdural taps showed nothing unusual. Reports of the blood chemistry were as follows: nonprotein nitrogen 50 mg./100 cc., and later 28 mg./100 cc., serum sodium 164 mEq./l., serum chlorides 128 mEq./l., potassium 4.5 mEq./l. and carbon dioxide combining power 18 mEq./l. Diagnoses of milk allergy, pyloric stenosis and brain abscess were entertained but not verified, and he was discharged (against advice) after 4 mo. hospitalization with a weight of 2.7 kg.

The following day he was admitted to the hospital. He was markedly undernourished and dehydrated and weighed 2.7 kg. Temperature was 39.1° C. He was alert but irritable and the turgor of the skin was poor. There was no generalized adenopathy. Anterior fontanel was depressed. Eyes, ears, nose and throat appeared normal. Neck was supple. Lungs were clear to auscultation and percussion. There was a Grade II systolic murmur best heard at the left 4th intercostal space.

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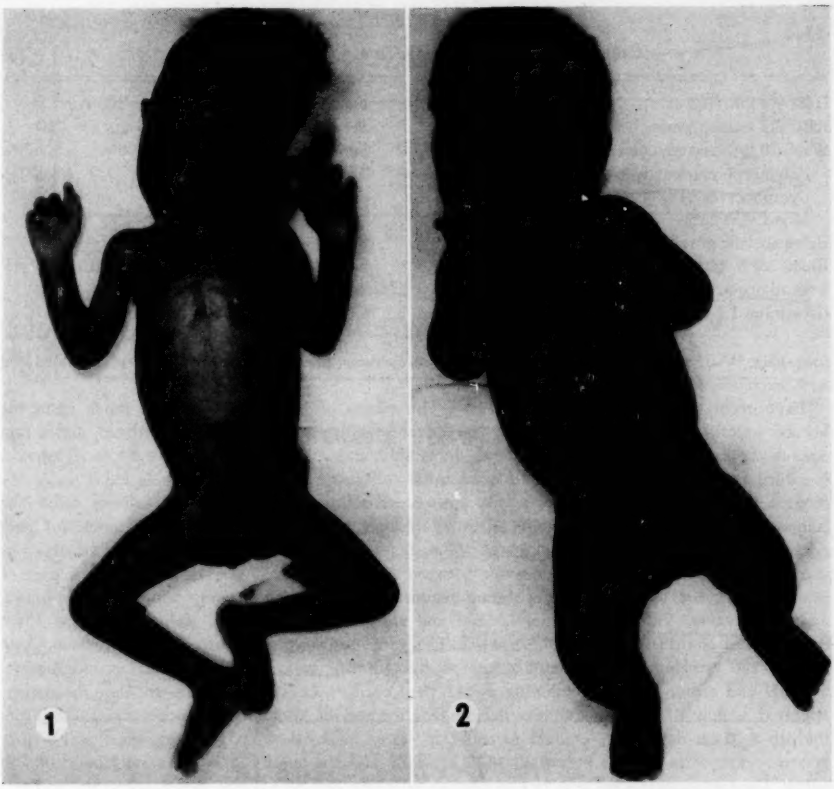

FIG. 1. On admission, G.M., 6½ mo. old Negro male, weighing 2.7 kg. with vomiting, dehydration and persistent fever.

Fig. 2. At discharge from hospital, G.M., 8½ mo. old, weighing 5.5 kg., well hydrated and no vomiting or fever.

Heart was not enlarged to percussion and the blood pressure was 80/50 mm.Hg. Abdomen was distended but there were no masses or tenderness. Liver, spleen and kidneys were not palpable. Genitalia appeared normal. There were no abnormal neurologic findings.

PROGRAM OF STUDY

Control Period: The laboratory data during this period are shown in table 1. The significant findings were elevated values for nonprotein nitrogen, serum sodium and chloride, and low specific gravity of the urines. The blood Kahn test was negative and tuberculin tests showed no reaction. Several blood cultures as well as agglutinations for many pathogens were negative. Roentgenograms of the skull, long bones, chest, gastrointestinal tract and intravenous and retrograde pyelograms were normal. Oral glucose and epinephrine-glucose tolerance tests gave normal results. The output of 17-ketosteroids was 0.58 mg./24 hr. Thymol turbidity test was normal. During this period of observation, the patient was irritable, vomited repeatedly and was constipated; the dehydration was severe enough to necessitate frequent intravenous infusions; the temperature fluctuated between 36.6° and 40.0° C. Daily output of urine varied between 800 and 1250 cc. depending upon the total intake of fluids and the amount of vomiting. The specific gravity of urines ranged from 1.007 to 1.010. The amount of vomiting was not influenced by the nature or composition of the milk

TABLE 1

LABORATORY DATA OBTAINED DURING CONTROL PERIOD

Hgb. 9.4 gm./100 cc.	Fasting blood glucose 57 mg./100 cc.
RBC 3.2 million/cmm.	Serum calcium 11.2 mg./100 cc.
WBC 10.0 thousand/cmm.	Serum phosphorus 4.9 mg./100 cc.
Polymorphonuclear leucocytes 46%	Total protein 7.1 gm./100 cc.
Lymphocytes 41%	Albumin 3.6 gm./100 cc.
Monocytes 13%	Globulin 3.5 gm./100 cc.
Urine specific gravity 1.010 to 1.007	Serum sodium 160 and 175 mEq./l.
Blood NPN 44 mg./100 cc.	Serum potassium 5.26 and 5.43 mEq./l.
Urea nitrogen 25 mg./100 cc.	Serum chlorides 128 and 125 mEq./l.
Creatinine 1.1 mg./100 cc.	CO_2 combining power 26.6 mEq./l.

formulae. With freely administered fluids, an intravenous phenolsulfonphthalein test demonstrated 85% excretion of the dye in 2 hr.

Experimental Period: 1. Hydration Test.—The effects of increasing intake of fluids upon the urinary output, specific gravity of urine, weight, body temperature, nonprotein nitrogen, and serum sodium, potassium and chloride are shown in table 2 and chart 1. The infant was placed upon a Bradford frame for 11 days and total daily urine collections were made. He was fed (via gastric tube) a mixture of evaporated cow's milk with added solids approximating 863 calories daily. The composition of the diet was protein 32 gm., carbohydrate 105 gm., fat 35 gm., sodium 0.7 gm., potassium 1.79 gm. and chloride 1.29 gm. The daily intake of fluids began with 850 cc. and was gradually increased, by addition of water between feedings, to 2235 cc. During the 1st 4 days of limited fluids, the results of a dehydrating regimen were noted in a rising temperature, vomiting and constipation. Values for serum sodium and chloride were elevated: sodium 194.4 to 159.2 mEq./l., and chlorides 170 to 125.5 mEq./l. The value for nonprotein nitrogen ranged from 53 to 65 mg./100 cc. Hematocrit determinations on the 4th day indicated moderate hemoconcentration. The pH and carbon dioxide combining power were normal. At the end of the 4th day, the patient appeared acutely ill, restless and very dehydrated; the specific gravity of the urine was 1.011. From the 5th to 11th days, with gradual increases in water intake between feedings, there was a progressive increase in urinary output to 1620 cc. daily and the specific gravity varied from 1.006 to 1.000. The temperature gradually fell to normal, vomiting diminished and values for serum sodium, chloride and nonprotein nitrogen approached normal. The patient was more alert, playful, appetite was increased and he was no longer constipated.

TABLE 2

HYDRATION TEST SHOWING EFFECT OF INCREASING INTAKE OF FLUIDS UPON URINARY OUTPUT, SPECIFIC GRAVITY OF URINE, WEIGHT, BODY TEMPERATURE, NONPROTEIN NITROGEN AND SERUM SODIUM, POTASSIUM AND CHLORIDE

Day	Intake (cc.)	Output (cc.)	Specific gravity	Weight (kg.)	Temp. (°C.)	Sodium mEq./l.	Potassium mEq./l.	Chloride mEq./l.	NPN mg./100 cc.
1	850	800	1.007	3.03	39.4	175.3	5.43	125.5	53
2	945	570	1.009	2.96	39.5	194.6	6.11	170.0	63
3	960	450	1.007	3.04	39.8	159.2	—	125.5	65
4	960	520	1.011	3.18	40.1	165.2	—	132.0	64
5	1455	1030	1.005	3.25	38.9	157.2	5.54	119.0	57
6	1645	1125	1.005	3.27	38.3	152.0	—	120.0	44
7	1785	1295	1.004	3.29	38.6	163.1	5.1	120.0	49
8	1560	940	1.006	3.20	37.3	—	—	—	—
9	1845	1150	1.005	3.31	37.6	154.1	—	94.6	45
10	1804	1310	1.005	3.32	37.6	157.9	4.7	107.0	44
11	2235	1620	1.000	3.36	37.8	154.2	—	101.7	38

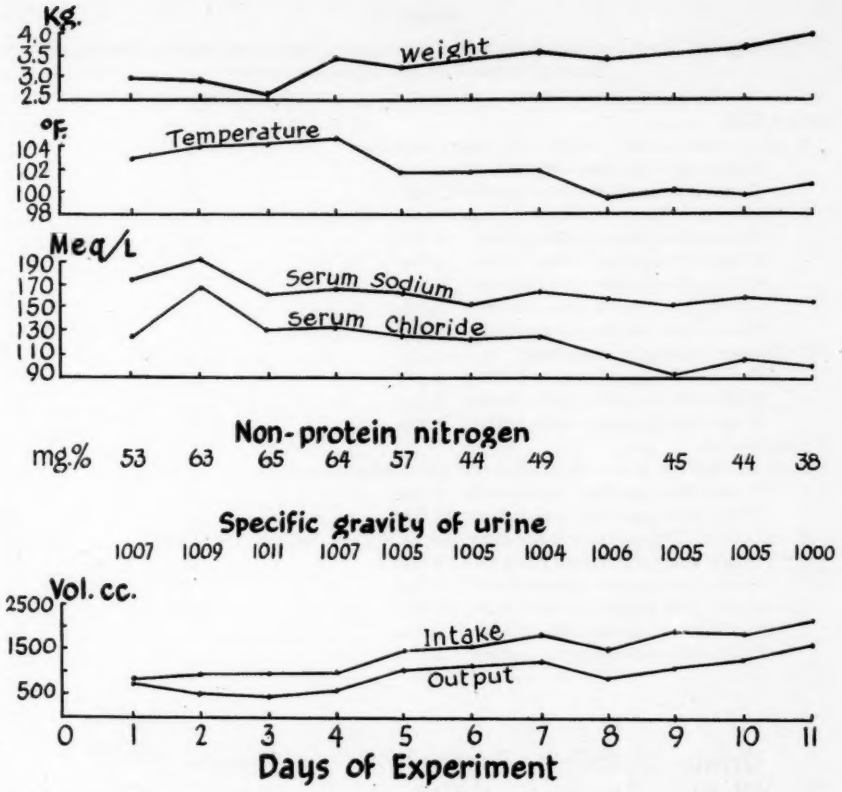

CHART 1. Hydration test showing effect of increasing intake of fluids on weight, temperature, values for serum sodium and chloride and nonprotein nitrogen, and specific gravity of urine.

2. Carter-Robbins' Test.[4]—The effect of intravenous hypertonic saline upon the output of urine is shown in table 3 and chart 2. Fluids were withheld for 8 hr. prior to the test. Then 20 cc. water/kg. body weight was administered orally over a 1 hr. period and urines collected 30 and 45 min. after ingestion of water. The volume and specific gravity were determined. At the end of the 45 min. period, intravenous infusion of 2.5% sodium chloride at the rate of 0.25 cc./kg. body weight/min. for 45 min. At the completion of the intravenous infusion, urine volumes were determined at 15, 30, 45, 60 and 75 minutes. Pitressin (0.1 unit) was then given intravenously and urine volumes determined at 15, 30 and 45 minutes after injection. The control for the test was a normal 3 mo. old Negro female who had recovered from an upper respiratory infection and who had normal renal function.

The normal response, as shown by the control, was a prompt and marked decrease of urine flow for 30 min. during the infusion of hypertonic saline. The moderate rise at the end of the infusion was still well below the maximum urine flow during the pre-infusion period. Moreover, at the end of the observation period (120 min.) the output of urine was still below pre-infusion volumes. It was not considered necessary to inject pitressin intravenously in view of the normal antidiuretic response during the infusion of hypertonic saline. In contrast, no antidiuretic response was noted in the patient during or after the infusion of hypertonic saline. The minute output of urine during the control period was still below the recommended volume for the test[4] and was probably the result of the preceding dehydration prior to the test. During the infusion period, the

TABLE 3

CARTER-ROBBINS' TEST SHOWING EFFECT OF INTRAVENOUS HYPERTONIC SALINE UPON OUTPUT OF URINE (PATIENT G.M. AND NORMAL CONTROL)

Patient G.M.	
A. 20 cc. water/kg. body weight orally over 1 hr. period.	
30 min. after ingestion, urine volume	4 cc.
45 min. after ingestion, urine volume	1.2 cc.
B. Infusion of 2.5% sodium chloride intravenously (0.25 cc./kg./min. for 45 min.).	
15 min. after infusion, urine volume	6.0 cc.
30 min. after infusion, urine volume	16.0 cc.
45 min. after infusion, urine volume	10.4 cc.
60 min. after infusion, urine volume	6.0 cc.
75 min. after infusion, urine volume	4.0 cc.
C. Pitressin (0.1 unit) intravenously	
15 min. after injection, urine volume	4.4 cc.
30 min. after injection, urine volume	3.8 cc.
45 min. after injection, urine volume	1.9 cc.
Normal Control	
A. 20 cc. water/kg. body weight orally over 1 hr. period.	
30 min. after ingestion, urine volume	6.0 cc.
45 min. after ingestion, urine volume	22.0 cc.
B. Infusion of 2.5% sodium chloride intravenously (0.25 cc./kg./min. for 45 min.).	
15 min. after infusion, urine volume	9.0 cc.
30 min. after infusion, urine volume	0.5 cc.
45 min. after infusion, urine volume	15.0 cc.
60 min. after infusion, urine volume	3.0 cc.
75 min. after infusion, urine volume	1.5 cc.

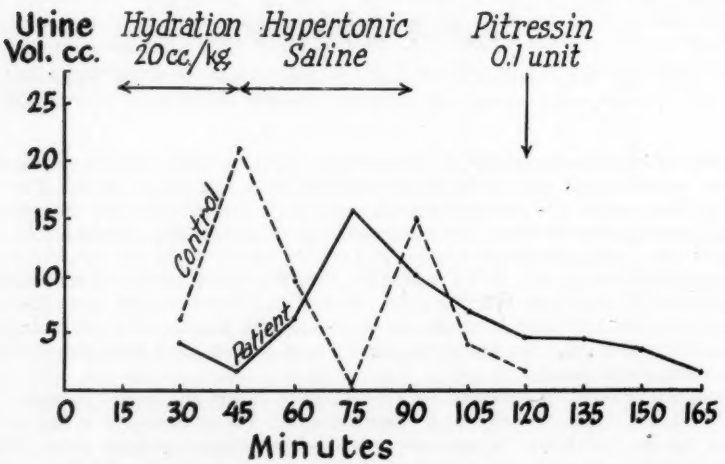

CHART 2. Carter-Robbins' test in patient and normal control. Normal response is shown in control with marked reduction of urinary output following infusion of hypertonic sodium chloride solution. There was no antidiuretic response in patient following hypertonic sodium chloride or pitressin.

TABLE 4

PITRESSIN TEST SHOWING EFFECT OF PITRESSIN ON SPECIFIC GRAVITY AND VOLUME OF URINE

Time (hr.)	Urine volume (cc.)	Specific Gravity
½	57	1003
1	14	1003
1½	15	1004
2	7	1004
2½	19	1005
3	20	1003
3½	28	1003
4	50	1003
	Pitressin (2 units) at end of 4 hr.	
4½	72	1004
5	37	1005
5½	27	1004
6	21	1003
6½	25	1003
	Pitressin (4 units) at end of 6½ hr.	
7	48	1005
7½	65	1003
8	45	1003
8½	68	1004
9	28	1003
9½	15	1004

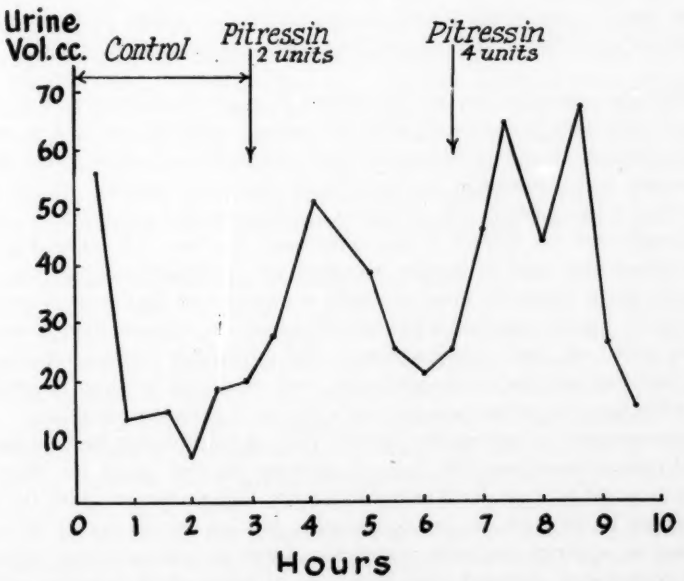

CHART 3. Pitressin test showing lack of response to as much as 4 units pitressin intramuscularly.

minute output of urine increased markedly and did not fall below pre-infusion values. Similarly, 0.1 unit pitressin did not materially alter the output of urine in this patient. The low value at the end of the test could be explained perhaps on the basis of dehydration, since at this time the patient appeared lethargic and was irritable when disturbed.

3. Pitressin Test.—The effect of pitressin upon the specific gravity and volume of urine is shown in table 4 and chart 3. The patient was well hydrated prior to the test. Urine was obtained by catheter every half hour for 4 hr.; volume and specific gravity were determined, and this served as the control. Two units of pitressin were administered intramuscularly and urines were collected in a similar manner for 2½ hr. Four units of pitressin were given at this time because of the lack of response to the previous dose and urines were collected for another 2½ hr. It will be seen from the data that pitressin, in amounts up to 4 units intramuscularly, did not affect either the output of urine or the specific gravity. The last dose produced blanching and abdominal cramps with loose stools, and was considered "toxic" for this patient.

Discussion

While polyuria and polydipsia are common to all varieties of diabetes insipidus, many factors have been discussed in the pathogenesis of this disease. In general, diabetes insipidus may be produced by lesions involving the supraoptic nuclei, the posterior lobe of the hypophysis or the supraoptic-hypophyseal tract anywhere between these two areas. This organic type of diabetes insipidus usually responds to pitressin therapy. Diabetes insipidus of idiopathic origin constituted the largest group of cases observed by Blattner.[5] In two such cases studied at autopsy, atrophy of the posterior pituitary was considered secondary to a lesion in the supraoptic nuclei and supraoptic-hypophyseal tract; the anterior lobe of the pituitary was intact. The interpretation of such findings is consistent with the modern theory of diabetes insipidus that the fundamental pathology is the degeneration or destruction of the supraoptic-hypophyseal system which regulates water balance in the presence of a normally functioning anterior lobe of the pituitary. Diabetes insipidus may be recognized in early infancy, is associated with fever, vomiting, dehydration and constipation, and may not be responsive to administered posterior pituitary extract.

Polyuria and polydipsia may be encountered in many other diseases of infancy and childhood. One must consider congenital and acquired renal diseases such as congenital polycystic kidneys, chronic pyelonephritis, glomerulonephritis, hydronephrosis associated with bladder neck obstruction, ureterocele and obstructing aberrant vessels. Diabetes mellitus may cause polyuria and polydipsia, and the presence of glycosuria, acetonuria and hyperglycemia are helpful in the differential diagnosis. The clinical picture of marked dehydration, loss of weight, vomiting and circulatory collapse may simulate Addisonian crisis. However, there is usually a reduction in the levels of sodium and chloride while that of potassium is elevated. Moreover, the administration of water alone does not correct the electrolyte disturbance. The relationship between other glands of internal secretion and diabetes insipidus has been considered by many investigators[6–12] but the effect upon the polyuria and polydipsia appears of secondary importance.

Previous attempts to attribute this patient's fever and dehydration to a systemic infection had been unsatisfactory. No focus of infection was ever found and there was no response to varied and prolonged antibiotic therapy. Various tests ruled out the common renal diseases as the cause for excessive diuresis and low specific gravity of the urine. There was no apparent endocrine disturbance. Later, the clinical course suggested an unusual syndrome of abnormal water balance in an infant which resembled neurohypo-

physeal diabetes insipidus but which did not respond to pitressin. Such a syndrome was described in 1945 by Waring, Kajdi and Tappan[1] as a congenital defect of water metabolism and was characterized by (1) onset shortly after birth, (2) erratic and unexplained fever, (3) persistent constipation, (4) vomiting (during the first 3 months of life), (5) polydipsia and polyuria, which did not respond to pitressin, (6) high values for serum sodium and chloride, (7) high skin resistance, (8) rapid dehydration if fluids are reduced or withheld, (9) inability to excrete urine of a high specific gravity, (10) familial incidence and (11) occurrence in boys only(?). The familial and sexual incidence of this disease was stressed by Williams and Henry[2] in 1947 in a report of seven similar cases in one family for five generations. The disease occurred only in males, was transmitted by females and appeared to be a sex-linked, recessive characteristic. One of these cases, a 35 year old physician, was studied when he was admitted to the hospital because of pneumonia. He had had symptoms of diabetes insipidus since the first month of life and had enjoyed relatively good health as long as he drank water freely. His symptoms were not controlled by pitressin. Twice, when fluids were withheld, circulatory collapse developed. The levels of serum sodium and chloride were normal or slightly elevated. That this syndrome may not be limited to males, or that there need not be elevated values for sodium and chloride is observed in the report of Dancis, Birmingham and Leslie[3] who described a 6½ month old female with recurrent episodes of fever shortly after birth. The temperature could be elevated or reduced by altering the intake of fluids. Here, too, pitressin exhibited no antidiuretic effect.

Limitation of fluids during the "control period" as well as during the first four days of the "hydration test" resulted in a persistence of fever, vomiting and constipation. Also, values for nonprotein nitrogen, serum sodium and chloride were notably elevated. Satisfactory hydration was maintained after the total fluid intake exceeded 2000 cc. daily, and with such therapy alone there was a subsidence of fever, vomiting and constipation, and a return to normal levels of nonprotein nitrogen, serum sodium and chloride. From a practical point of view, such a regimen is difficult for a young infant who is disturbed every 3 or 4 hours for food and/or water over the whole 24 hours. However, this patient is being observed with a total fluid intake of about 2150 cc. daily; the temperature remains normal or slightly elevated; there is no vomiting or constipation; the values of serum sodium and chloride are normal. His weight at 8½ months of age is 5.5 kg. (double that at 6½ months) and he is playful and has a good appetite (Fig. 2).

One the basis of investigations by Gilman and Goodman,[13-14] who found that dehydration as well as oral administration of hypertonic saline led to the appearance of antidiuretic substance in the urine of normal but not of hypophysectomized rats, Carter and Robbins[4] devised a test (Carter-Robbins' test referred above) in which the response to intravenous infusion of 2.5% sodium chloride was employed to differentiate between diabetes insipidus and psychogenic polydipsia in adult patients. Recently, Verney[15] made extensive observations on the absorption and excretion of water and the antidiuretic hormone. Using varying concentrations of sodium chloride intravenously, he determined that the inhibition of urinary flow was not due specifically to sodium chloride but was due to the rise in osmotic pressure brought about by hypertonic solutions of sodium chloride. Compared to a normal control, the present authors' patient did not exhibit the antidiuretic effect of intravenous infusion of hypertonic saline, nor was

there any response to intramuscular administration of pitressin to the point of toxicity. Moreover, in the patient reported by Williams and Henry,[2] neither the serum nor the body cells were found to inactivate pitressin more rapidly than normal. Furthermore, bio-assay methods by Dancis and associates[3] disclosed that antidiuretic substance was present in significant amounts in the patient's urine. It would seem that, while the hormonal mechanism of these patients is intact, the resistance to administered pitressin is probably the result of some defect in end-organ response of the kidney.

Careful studies[16-23] of the renal function in diabetes insipidus have revealed one important abnormality—the lack of reabsorption of water in the renal tubules. That the function of reabsorption of water by the kidney tubules is disturbed in diabetes insipidus and may be corrected with the administration of pituitrin has been shown also by experimental procedures[24-26] in which pituitrin and its effect on the kidney have been studied in mammals and in amphibians. On the basis of his observations on the effect of pituitary extract on urea excretion, Poulsson[27] concluded that the proximal portion of the tubule was the site of the antidiuretic action. Later, studies by Gersch and Stieglitz[28] and Gersch[29] indicated that the loop of Henle, and less so the proximal convoluted tubule, was the site of action of pituitary extract. Burgess, Harvey and Marshall[30] arrived at similar conclusions from their experiments on animals and fish. They observed a typical antidiuretic effect only in mammals that have a loop of Henle, but found no such response in amphibians or in fish because they do not have a loop of Henle. While the present authors' studies in this patient have been limited to the exclusion of the common congenital and inflammatory renal diseases, more complete studies by others[1-3] have shown that such patients have an abnormality in renal tubular function. In the absence of a disturbance in the supraoptic-hypophyseal system, or other endocrinopathy, the failure of antidiuretic response to pitressin in these cases may well be a reflection of end-organ (loop of Henle) deficiency in the kidney.

Summary

The present authors have presented the report of a 6½ month old Negro male who, shortly after birth, developed polyuria, polydipsia, fever, vomiting, dehydration, constipation and failure to gain weight.

Investigations ruled out systemic infections as well as the common inflammatory and congenital renal diseases.

Under "control" conditions (average fluid intake) there was a persistence of the fever, vomiting and constipation; the values for nonprotein nitrogen, serum sodium and chloride were elevated above normal. The polyuria, which was characterized by low specific gravity, rose to a value of 1.011 during periods of marked dehydration.

During the "hydration test," a progressive increase of fluid intake above 2000 cc. daily resulted in normal temperature, absence of vomiting, increase of weight, and normal values for nonprotein nitrogen, serum sodium and chloride.

There was no antidiuretic response either to intravenous infusion of hypertonic saline (Carter-Robbins' test) or to 0.1 unit pitressin intravenously. A normal control showed prompt antidiuresis during and following the infusion of hypertonic saline.

Intramuscular administration of pitressin to the point of toxicity (4 units) had no effect on the volume or specific gravity of the urine.

It is postulated that this syndrome of diabetes insipidus in infancy, resistant to pitressin, is the result of a failure of end-organ response in the kidney.

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SPANISH ABSTRACT

Diabetes Insípida en la Infancia Resistente a la Pitresina

Este caso se refiere a un negrito de seis meses y medio de edad que inmediatamente después del nacimiento presentó poliuria, polidipsia, fiebre, vómitos, deshidratación, constipación y estacionamiento de peso. Se eliminaron como causas de este cuadro infecciones generales y alteraciones renales congénitas diversas. Con la administración de líquidos en cantidades normales, persistieron la fiebre, los vómitos y la constipación; asímismo, las cifras de nitrógeno no proteico, sodio y cloro en sangre sobrepasaban los límites normales y en la orina, la gravedad específica, generalmente baja, se elevaba a 1011 al acentuarse la deshidratación.

Con la prueba de hidratación consistente en el aumento progresivo de líquidos a más de dos litros en 24 horas, se obtuvieron temperatura normal, desaparición de los vómitos, aumento de peso, y cifras normales de nitrógeno no proteico, cloro y sodio.

No se observó respuesta antidiurética a la administración intravenosa de suero salino hipertónico (Prueba de Carter-Robbins) o a la de 0.1 de unidad de Pitresina; un niño control sí la mostró con el suero hipertónico. La administración intramuscular de 4 unidades de Pitresina (cantidad considerada tóxica) no tuvo ningún efecto sobre el volumen y la gravedad específica de la orina.

Se supone que este síndrome de diabetes insípida en la infancia, resistente a la Pitresina, es el resultado de una anormalidad fisiológico del asa de Henle.

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GROWTH IN HEAD WIDTH DURING THE FIRST TWELVE YEARS OF LIFE

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IN NORTH AMERICAN pediatric and obstetric periodicals, few topics have a longer history than head size. This is true not only with respect to description of unusual cases, but also in regard to presentation of normative studies. Publication of clinically useful "frames of reference" extends from the 1843 report on head length and breadth by Meigs[1] to the recent investigations on head circumference by Boyd.[2, 3]

The present paper pertains to one aspect of head size—head breadth or width. It reports findings from three series of original data[4–6] and systematizes the results from more than 50 unpublished[7, 8] and published[1, 9–60] studies.

Major aims are:

1. To colligate the presently available investigations of biparietal diameter for non-pathologic North American infants and children.
2. To examine the anthropometric comparability of the investigations and appraise their data from the standpoint of morphologic validity.
3. To present a synthesis of research findings on North American white boys and girls, i.e., to supply for each sex highly dependable statistics on head width at ages from birth to 12 years.
4. To compare North American white, Negro, Chinese, Japanese, and Mexican children with reference to average biparietal diameter.
5. To describe and extend present knowledge regarding the growth of individual children in breadth of head.
6. To discuss relationships between head width and other morphologic traits.

METHODOLOGIC CONSIDERATIONS

Definitions of Head Width: As Tildesley[61] has stated aptly: "One of the cardinal principles of anthropometry . . . is that . . . before using for comparative purposes data published by others, one must always look up their own definitions of the measurements they record, to see whether the various records are in fact comparable." The definitions of head width given in different studies seem to be "in fact comparable." While there is considerable variation in degree of specificity and choice of language, it appears tenable to infer that the somatic characteristic under description is the same throughout.

Forms of definition include (1) largest biparietal diameter or measurement,[9, 13] (2) maximum transverse breadth or width of head,[5, 14–18] (3) greatest straight line distance between the parietal eminences or protuberances,[1, 8, 19, 20] (4) bi-eural diameter, euryon to euryon, or distance between the two points on the head which form the termini of the line of greatest breadth,[21–23] (5) maximum transverse breadth of the head in the horizontal plane,[24–29] (6) greatest width between the parietal eminences, perpendicular

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to the midsaggital plane,[30,31] (7) largest transverse measurement above the external auditory meati[32,33] and (8) greatest diameter at right angles to a saggital plane and superior to the zygomatic processes and supramastoid crests.[4,6,33-39]

Instruments Used: In almost all instances, the anthropometric tool used to measure head width has been some type of outside, graduated, hinge or spreading calipers. Several studies indicate the make or model of spreading instrument that was utilized, e.g., Hermann,[16] Hrdlicka,[4-6,18,34-36] Martin,[8,21] Siegelting,[13] "similar to Broca's head-calipers,"[40] "a pelvimeter."[12,41] One study appears to have employed ungraduated outside calipers in conjunction with a metric ruler;[24] another used aluminum, broad-arm, sliding calipers.[5] Spreading calipers, having small contact areas, readily separate the head hair and compress the scalp integument; in the case of the series of data obtained with sliding calipers, comparable measurement conditions were attained since the subjects had little hair (infants) and the instrument was read "using a firm pressure."

Reliability of Data: Head width investigations encompass the gamut on the matter of discussing the dependability of their records. Some omit any mention of the topic, some make a general statement on rigorousness of the measurement procedure, and some present quantitative findings for reliability.

Sample notations relating to carefulness in data collection are: (1) the subjects were "carefully measured,"[10] (2) the measurements were taken with "the most scrupulous caution,"[9] (3) "careful attention was given to the maintenance of high standards of anthropometric work"[28] and (4) "every effort was made to overcome unreliability."[42]

Goodman and Meredith[4] investigated the reliability of head width data using 120 neonates measured on the day of birth. For 97% of the subjects, the independent records of two anthropometrists did not differ by more than 0.1 cm. In terms of the Pearson product-moment method of correlation, the paired measures (120 for each anthropometrist) gave a reliability coefficient of $r = .98$.

A companion study on 94 children in their fifth postnatal year was made by Potter and Meredith.[43] Here the reliability coefficient was $r = .99$, indicating "extremely high consistency" between the records obtained by two anthropometrists working separately.

From "repeated measurements on 42 individuals," Herskovits[21] found that his first measurements differed from his second by an average of 0.04 cm. Further, on a series of 100 boys, he derived a "mean square deviation" of 0.13 cm. from the differences between his measures and those of another anthropometrist.

Cates and Goodwin[20] arranged for three anthropometrists to each take 30 measurements of head width on one subject. Measuring was "done at one sitting and an independent observer read the instrument and noted the result each time." The records of one worker varied from 9.9 cm. to 10.0 cm. and "the other workers showed . . . no greater variability."[20]

In a study by Boas[40] it is reported that several anthropometrists each measured biparietal diameter on 13 heads. In relation to the average width for each head, less than 3% of the measures differed more than 0.1 cm.

Bayley[23] used an indirect estimate of the reliability of head width data. She obtained "coefficients of correlation between measures taken at adjacent age levels." The mean of the r's was .93, leading to the inference that on making allowance for "the growth changes which occur from one age to the next, the measures appeared to be very reliable."[23]

Taken together, the above materials show that research records for head width are highly reliable.

Validity of Neonatal Measurements

This section treats the special problem of the amount by which morphologic head width is mechanically distorted as a consequence of the birth process. It assembles research findings that have direct or indirect bearing on the question: To what extent does head molding associated with parturition affect the biologic validity of records for biparietal diameter taken at birth?

Calkins[32] secured an estimate of mean head width for full term infants *in utero* by measuring a small series of subjects largely free from birth molding. The series comprised 27 full term, living infants from two types of birth: (1) cesarean section, without previous occurrence of labor pains and (2) breech extraction, where the extraction was easily and quickly performed. The mean of measurements taken on the day of birth was 9.7 cm., or 0.4 cm. higher than the mean at birth for the general run of North American white infants.* The probability that this obtained difference (0.4 cm.) does not underestimate the average amount of mechanical narrowing is strengthened by Calkins' statement that in making his measurements "a very slight uniform pressure was used . . . with the idea of entirely avoiding compression."[32]

Lateral expansion of the head during the first week following birth has been studied by Tiber,[8] Goodman and Meredith,[4] and Freeman and Platt.[44] All used normal, full term infants without regard to type of birth. Tiber measured the same 208 infants within six hours after birth and one week later; similarly, Goodman and Meredith measured the same 68 infants on the day of birth and one week later. In each study the mean at one week exceeded the mean at birth by 0.1 cm. Freeman and Platt measured 312 infants on the day of birth and remeasured 149 at the end of the first week. Their mean at birth was 0.2 cm. lower than that at one week.

Bakwin and Bakwin[30] compared head width means from records made between the first and third days of postnatal life and records distributed over the first week. They found that the mean for the first three days "showed no difference from the mean for the first seven days."[30]

Generalizing from the foregoing studies: (1) it is estimated that birth molding does not reduce head width by an average of more than 0.4 cm., and (2) 0.15 cm. may be taken as a close approximation of average increase in head width during the first postnatal week.

Means for Head Width

Although the focal interest of this paper is growth in biparietal diameter between birth and 12 years, perspective will be gained by antecedent reference to growth during prenatal life. Scammon and Calkins[19] studied a series of 369 white fetuses "selected from a much larger group by discarding all soft and distorted specimens." The specimens were amassed "from the Minnesota General Hospital, the Elliott Memorial Hospital of the University of Minnesota, and similar local institutions."[19]

Direct sorting of the head width records by age was not possible "since few of the specimens were accompanied with clinical histories from which age could be estimated with accuracy."[19] Alternatively, groups were formed in terms of crown-heel length, the mean width of head was computed for each stature group, and the resultant head-width-for-stature means were converted to head-width-for-age equivalents.

It was found that at the termination of one-fourth, one-half and three-fourths of

* The manner of deriving the latter mean will be taken up in the next section.

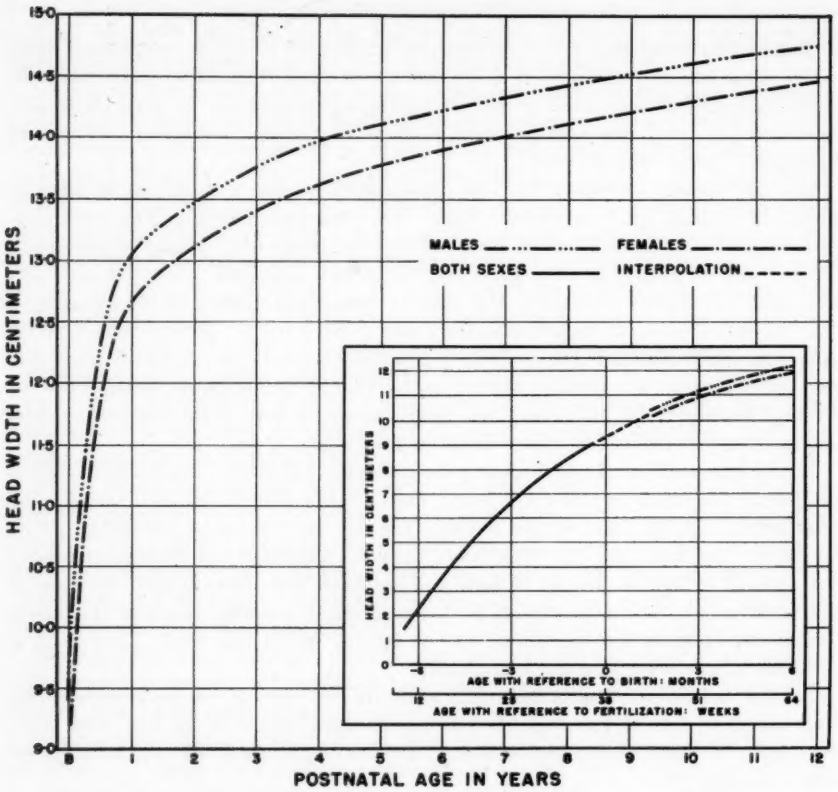

CHART 1. Graph showing course of growth in head width from early prenatal life to 12 yr. of age. Curves beginning at lower left are drawn to composite means for boys and girls from table 3. Inset reproduces mean trend for fetal period from Scammon and Calkins, projects this trend in manner estimated to represent growth in head width free from birth molding, and continues with segments of postnatal mean trends from table 3.

prenatal life biparietal diameter averages 1.4 cm., 4.8 cm. and 7.5 cm., respectively. The trend line obtained from graphing Scammon and Calkins' means for successive fetal months is reproduced in the inset portion of chart 1.

Turning now to the first 12 postnatal years, it is of historic interest that in 1843 Meigs,[1] who "knew of no measurements taken in this country," reported having determined biparietal diameter of 150 infants of both sexes "born at term, in the city of Philadelphia." The mean obtained was "3 inches, 11 lines."[1]

Nearly four hundred means have been assembled on samples of North American children representing quarterly ages between birth and 6 months, biannual ages between 6 months and 2 years, annual ages between 2 and 4 years, and biennial ages between 4 and 12 years. Table 1 presents the means for boys and table 2 those for girls.* It will be seen that each mean is accompanied by the N (number of subjects measured) and by a figure identifying the investigation from which it was drawn.

* Means derived from less than 10 records were not tabled.

TABLE 1

HEAD WIDTH (CM.): MEANS FOR 193 SAMPLES OF NORTH AMERICAN BOYS STUDIED AT SELECTED AGES FROM BIRTH TO 12 YEARS. UNLESS OTHERWISE INDICATED, EACH SAMPLE REPRESENTS WHITE BOYS

Birth			3 months			6 months			1 year		
Study	N	Mean	Study	N	Mean	Study	N	Mean	Study	N	Mean
32*	18	9.8†	35(33)***	47	11.4§	38	155	12.4†††	38	74	13.2†††
9	330	9.6	5	121	11.4§	5	225	12.3§	16(34)***	15	13.1§
4	60	9.6‡	28	13	11.2	7	50	12.2§	35(33)***	114	13.1§
42	28	9.5§	38	163	11.2†††	35(33)***	87	12.2§	23	28	13.1§
44	163	9.4**	7	50	11.1§	23	30	12.2§	5	246	13.1§
11	407	9.3	23	31	11.1§	29	155	12.2§	28	22	13.0
8	106	9.3	29	148	11.1§	38	46	12.2‡‡	29	164	13.0§
30	818	9.3	38	48	11.1‡‡	28	18	12.1	38	21	13.0‡‡
20	346	9.3††	45	50	11.0**	45	34	12.1**	31	41	12.9
11	362	9.1‡‡	31	94	11.0	46	19	11.9	45	19	12.8**
12	1000	8.9§§	46	19	10.8	31	85	11.8	46	19	12.8

* Each study is identified according to its numeric position in the list of references.
† Born without head molding.
‡ Infants of northwest European ancestry and low economic status.
§ Infants of northwest European descent and above-average socioeconomic level.
** About two-thirds of subjects white, one-third American Negro.
†† Neonates measured about 12 days after birth: mean reduced from 9.5 cm. to the estimated figure for "birth."
‡‡ American Negro infants.
§§ "Jewish, Italian and Slavic" ancestry predominating, some "Negroes, Turks and Asiatics" included.
*** To a considerable extent, the records of study 33 were incorporated in 35, and those of study 34 in 16.
††† Infants of the indigent and near-indigent classes given special dietary and health supervision.

TABLE 1 (*continued*)

18 months			2 years			3 years			4 years		
Study	N	Mean	Study	N	Mean	Study	N	Mean	Study	N	Mean
35(33)*	83	13.5†	34(16)*	16	13.8††	23	25	14.1†	34(16)*	34	14.2††
23	24	13.4†	23	24	13.8†	34(16)	28	14.0††	35(27)	102	14.2†
5	189	13.4†	35(33)*	81	13.7†	45	58	13.9††	23	21	14.2†
28	22	13.3	5	184	13.7†	35(27)*	89	13.9†	28	19	14.1
29	150	13.3†	28	22	13.6	18	35	13.9††	18	60	14.1††
45	14	13.2‡	45	41	13.6††	28	16	13.8	45	31	14.0††
22	170	13.2	29	163	13.5†	29	193	13.8†	13	24	14.0**
21	11	13.0§	22	162	13.4	13	32	13.7**	22	157	14.0
13	21	13.0**	21	17	13.3§	22	158	13.7	29	209	14.0†
			13	29	13.3**	21	27	13.5§	6	89	14.0
						37	50	13.4‡‡	37	50	13.8‡‡
									47	13	13.7§§
									21	42	13.6§

* To a considerable extent, the records of studies 27 and 33 were incorporated in 35, and those of study 16 in 34.
† Boys of northwest European descent and above-average socioeconomic status.
‡ About two-thirds of subjects white, one-third American Negro.
§ American Negro boys.
** Boys born prematurely; age adjusted for amount of prematurity.
†† Boys from professional and managerial families.
‡‡ Jewish boys of the "lower middle class."
§§ Boys of Mexican ancestry—*mestizo* in Texas and Mexico.

TABLE 1 (*continued*)

6 years			8 years			10 years			12 years		
Study	N	Mean	Study	N	Mean	Study	N	Mean	Study	N	Mean
40	36	14.5*	40	40	14.8*	15	28	15.0§§§	15	10	15.1§§§
45	22	14.4†	15	32	14.8§§§	40	92	14.9*	37	50	15.1††
35(27)‡	131	14.4§	18	51	14.7†	18	34	14.9†	40	132	15.0*
48	105	14.4**	35	166	14.6§	35	148	14.8§	45	34	14.9†
24	573	14.3	24	1997	14.5	24	1827	14.7	35	153	14.9§
40	47	14.3††	40	64	14.5††	40	209	14.7††	18	18	14.9†
25	43	14.3†	26	14	14.5****	34	173	14.7†	24	1531	14.8
34(16)‡	114	14.3†	25	89	14.5†	37	50	14.7††	40	358	14.8††
37	50	14.3††	34(16)‡	147	14.5†	17	92	14.7‡‡	25	90	14.8†
18	66	14.3†	37	50	14.5††	6	81	14.7	52	44	14.8††
17	52	14.3‡‡	48	118	14.5**	25	93	14.6†	34	247	14.8†
6	140	14.3	17	92	14.5‡‡	52	24	14.6††	17	98	14.8‡‡
22	168	14.2	6	127	14.5	45	31	14.6†	17	80	14.8§§
29	218	14.2§	52	18	14.4††	48	112	14.6**	51	110	14.7
17	40	14.2§§	45	14	14.4†	17	69	14.6§§	40	141	14.7§§
14	68	14.1	29	200	14.4§	14	139	14.5	26	63	14.7****
40	101	14.1§§	17	51	14.4§§	40	78	14.5§§	22	226	14.7
49	15	14.1	14	130	14.3	26	10	14.5****	48	118	14.7**
50	179	14.1	51	56	14.3***	49	117	14.5	29	201	14.7§
28	15	14.0	40	65	14.3§§	22	187	14.5	49	89	14.6
51	15	13.9***	49	62	14.3	50	689	14.5	50	708	14.6
21	96	13.9†††	22	164	14.3	29	170	14.5§	14	158	14.5
47	22	13.9‡‡‡	50	575	14.3	51	98	14.4***	51	93	14.5***
			52	29	14.2§§	53	103	14.3‡‡‡	52	37	14.4§§
			52	20	14.2††††	52	34	14.3§§	52	24	14.4††††
			47	19	14.1‡‡‡	52	22	14.3††††	47	33	14.4‡‡‡
			21	174	14.0†††	47	26	14.3‡‡‡	21	219	14.3†††
						21	116	14.2†††	53	101	14.2‡‡‡

* Boys of Bohemian ancestry, low economic status.
† Boys from professional and managerial families.
‡ The records of study 27 were incorporated in 35, and those of study 16 in 34.
§ Boys of northwest European lineage and above-average socioeconomic strata.
** Boys of Chinese (Cantonese) ancestry.
†† Jewish boys.
‡‡ Boys of Finnish ancestry, low economic level.
§§ Boys of Italian descent, low economic level.
*** Orphanage boys; two-fifths of Italian ancestry.
††† American Negro boys.
‡‡‡ Boys of Mexican lineage, low economic level.
§§§ Boys of Japanese descent.
**** Intellectually superior boys.
†††† Boys of Swedish descent.

Tables 1 and 2 do not carry the means reported by Chapin[10] and Ito[41]: these authors afford findings for both sexes together but not for each sex separately. The latter secured a mean of 9.4 cm. on 28 full term, American Japanese neonates born at Los Angeles; the former, a mean of 10.0 cm. at 3 months of age on 27 New York "hospital cases . . . many much below par."[10]

Having displayed the presently available materials on mean head width at the ages chosen, it is now possible to take two further steps:

1. To derive composite means for North American white boys and girls at each of the 12 ages studied.

2. To make comparative use of these composite values, referring to them the means from samples of nonwhite children and children of white subgroups.

Composite Means: The procedure in obtaining composite means to represent North

TABLE 2

HEAD WIDTH (CM.): MEANS FOR 176 SAMPLES OF NORTH AMERICAN GIRLS STUDIED AT SELECTED AGES FROM BIRTH TO 12 YEARS. UNLESS OTHERWISE INDICATED, EACH SAMPLE REPRESENTS WHITE GIRLS

Birth			3 months			6 months			1 year		
Study	N	Mean	Study	N	Mean	Study	N	Mean	Study	N	Mean
4*	60	9.5†	28	12	11.0	36(33)§§	90	12.0§	28	15	12.7
9	314	9.4	45	39	11.0‡	38	114	12.0***	45	20	12.7‡
44	149	9.3‡	36	42	11.0§	5	199	11.9§	13	14	12.7†††
8	102	9.2	5	109	11.0§	38	54	11.9††	31	59	12.7
30	835	9.2	38	123	10.9***	28	12	11.8	36(33)§§	95	12.7§
42	25	9.2§	38	59	10.9††	31	79	11.8	5	218	12.7§
11	372	9.1	31	104	10.8	23	28	11.8§	23	28	12.6§
20	327	9.1**	7	50	10.7§	45	44	11.7‡	29	146	12.6§
11	358	8.9††	23	30	10.7§	29	134	11.7§	38	50	12.6***
12	1000	8.8‡‡	29	122	10.7§	7	50	11.6§	38	26	12.6††
			46	15	10.5	46	15	11.5	46	15	12.4

* Each study is identified according to its numeric position in the list of references.
† Infants of northwest European ancestry and low economic status.
‡ About two-thirds of subjects white, one-third American Negro.
§ Infants of northwest European descent and above-average socioeconomic level.
** Neonates measured about 12 days after birth: mean reduced from 9.3 cm. to the estimated figure for "birth."
†† American Negro infants.
‡‡ "Jewish, Italian and Slavic" ancestry predominating, some "Negroes, Turks, and Asiatics" included.
§§ To a considerable extent, the records of study 33 were incorporated in 36.
*** Infants of the indigent and near-indigent classes given special dietary and health supervision.
††† Girls born prematurely; age adjusted to correct for amount of prematurity.

TABLE 2 (*continued*)

18 months			2 years			3 years			4 years		
Study	N	Mean	Study	N	Mean	Study	N	Mean	Study	N	Mean
36(33)*	67	13.1†	36(33)*	63	13.3†	18	15	13.7**	45	29	13.8**
5	195	13.1†	23	21	13.3†	36(27)*	74	13.6†	18	31	13.8**
28	17	13.0	5	138	13.3†	28	16	13.5	34(16)*	34	13.7**
23	24	13.0†	34(16)*	18	13.2**	34(16)*	27	13.5**	36(27)*	118	13.7†
29	139	12.9†	13	32	13.2‡	45	48	13.5**	23	23	13.7†
13	28	12.8‡	28	17	13.1	13	53	13.5‡	28	23	13.6
45	10	12.7§	29	161	13.1†	23	24	13.5†	22	154	13.6
22	163	12.3	21	12	13.0††	29	186	13.4†	29	223	13.6†
			45	39	12.9**	21	27	13.3††	21	29	13.5††
			22	156	12.6	22	149	13.3	13	26	13.5‡
									6	92	13.5

* To a considerable extent, the records of studies 27 and 33 were incorporated in 36, and those of study 16 in 34.
† Girls of northwest European descent and above-average socioeconomic status.
‡ Girls born prematurely; age adjusted for amount of prematurity.
§ About two-thirds of subjects white, one-third American Negro.
** Girls from professional and managerial families.
†† American Negro girls.

American white children appears best explained in terms of a specific example.* Reference to table 1 shows that at birth there are means for white boys from eight studies.[4, 8, 9, 11, 20, 30, 32, 42] First, each of these means was multiplied by its N; then, the eight products were summed and the eight N's were summed; finally, the former quantity was divided by the latter. The end result was a mean of 9.4 cm. from a total of 2,113 boys.

* Expression of the procedure as a generalized mathematic formula is accessible in an earlier publication (Meredith[62]).

TABLE 2 (*continued*)

6 years			8 years			10 years			12 years		
Study	N	Mean	Study	N	Mean	Study	N	Mean	Study	N	Mean
40	39	14.3*	40	44	14.4*	40	43	14.6*	40	41	14.7*
18	45	14.2†	15	33	14.4§§§	15	20	14.6§§§	52	44	14.7§
48	94	14.1‡	18	53	14.3†	24	1803	14.4	15	20	14.7§§§
24	609	14.0	24	1985	14.2	52	17	14.4§	24	1460	14.6
40	48	14.0§	40	54	14.2§	34	110	14.4†	34	126	14.6†
25	38	14.0†	26	15	14.2****	18	41	14.4†	18	22	14.6†
34(16)**	74	14.0†	25	78	14.2†	40	49	14.3§	40	51	14.5§
36(27)**	147	14.0††	52	17	14.2§	25	83	14.3†	26	45	14.5****
40	81	13.9‡‡	36	161	14.2††	45	19	14.3†	25	73	14.5†
45	32	13.9†	48	160	14.2‡	36	167	14.3††	36	150	14.5††
47	15	13.9§§	40	70	14.1‡‡	22	195	14.3	48	92	14.5‡
29	244	13.9††	34(16)**	100	14.1†	48	127	14.3‡	40	57	14.4‡‡
14	77	13.8	45	16	14.1†	40	60	14.2‡‡	49	114	14.4
28	15	13.8	29	212	14.1††	26	42	14.2****	45	12	14.4†
49	17	13.8	14	104	14.0	52	27	14.2††††	22	226	14.4
6	130	13.8	52	25	14.0††††	49	133	14.2	29	194	14.4††
13	23	13.7***	49	61	14.0	50	717	14.2	14	158	14.3
22	167	13.7	22	167	14.0	29	182	14.2††	52	31	14.3‡‡
50	196	13.7	50	576	14.0	14	140	14.1	52	28	14.3††††
51	10	13.6†††	51	42	13.9†††	52	28	14.1‡‡	50	745	14.3
21	70	13.6‡‡‡	52	22	13.9‡‡	6	78	14.1	51	14	14.1†††
			6	108	13.9	51	52	14.0†††	21	58	14.1‡‡‡
			21	87	13.7‡‡‡	53	89	14.0§§	47	31	14.1§§
			47	21	13.7§§	21	54	13.8‡‡‡	53	95	14.0§§
						47	22	13.7§§			

* Girls of Bohemian ancestry, low economic status.
† Girls from professional and managerial families.
‡ Girls of Chinese (Cantonese) ancestry.
§ Jewish girls.
** The records of study 16 were incorporated in 34, and those of study 27 in 36.
†† Girls of northwest European lineage and above-average socioeconomic strata.
‡‡ Girls of Italian ancestry, low economic level.
§§ Girls of Mexican descent, low economic level.
*** Girls born prematurely; age adjusted for amount of prematurity.
††† Orphanage girls, two-fifths of Italian descent.
‡‡‡ American Negro girls.
§§§ Girls of Japanese lineage.
**** Intellectually superior girls.
†††† Girls of Swedish ancestry.

Table 3 gives the composite means for boys and girls at each age studied. The statistical dependability of these means is high, i.e., the standard error of the mean is less than 0.03 cm. in every instance. Examination of table 3 shows:

1. The mean biparietal diameter of North American white boys is 9.4 cm. at birth, 13.1 cm. at 1 year, 14.0 cm. at 4 years and 14.7 cm. at 12 years.

2. Compared with the boys' means, those for girls are significantly smaller throughout. Equivalent means are obtained on boys 1 year of age and girls 2 years of age, on boys 7 years of age and girls 10 years of age.

3. The head width of the average North American white child is greater at 12 years of age than at birth by 5.3 cm. Expressed in relation to birth size, the head is broader at age 12 by approximately 57%.

4. One-half of the increase from birth to age 12 years takes place during the first 6 postnatal months. The exact course of the average trend over the whole period is portrayed graphically in chart 1.

Fleming[63] has published a major study of biparietal diameter on children 4 to 20 years of age living in Great Britain; the data were gathered between 1919 and 1932 on boys

TABLE 3

HEAD WIDTH (CM.): COMPOSITE MEANS FOR NORTH AMERICAN WHITE CHILDREN. COMPONENT SAMPLES WERE DRAWN FROM STUDIES MADE BETWEEN 1860 AND 1953

Age	Boys		Girls	
	N	Mean	N	Mean
Birth	2113	9.4	2035	9.2
3 mo.	686	11.2	607	10.9
6 mo.	824	12.2	721	11.9
1 yr.	723	13.1	640	12.7
1½ yr.	659	13.3	633	12.9
2 yr.	722	13.5	645	13.1
3 yr.	684	13.8	592	13.4
4 yr.	796	14.0	753	13.6
6 yr.	2093	14.2	1992	13.9
8 yr.	4221	14.4	3910	14.1
10 yr.	4467	14.6	3986	14.3
12 yr.	4685	14.7	3591	14.5

and girls of Welsh and English lineage, "a majority of whom were of Welsh stock."[63] For the age period 4 to 12 years, the means reported by Fleming and those of table 3 are identical.*

It also is of interest that identical means representing young adult males (15.3 cm.) were secured in the Fleming study and in the previously utilized North American studies by West,[14] Gray and Ayres[34] and Meredith.[35] On expressing the means for boys from table 3 in relation to this white adult value, it is found that approximately 60% of head width is attained by birth, 80% by 6 postnatal months, 90% by 3 years and 95% by 9 years.

Comparative North American Findings: From comparison of particular series of means in tables 1 and 2 with the appropriate composite values of table 3, it is found:

1. North American Negro children have narrower heads than North American white children. For all ages taken together, the 23 American Negro means average 0.2 cm. less than the means at corresponding ages from table 3. Differences between the separate pairs of Negro-white samples are statistically significant at birth on both sexes, at ages 3 to 12 on boys, and at ages 6 to 12 on girls.

2. North American school children of Japanese descent have wider heads than North American white school children. Tables 1 and 2 carry means for American Japanese boys and girls at ages 8, 10, and 12 years; these means exceed the like-age, white-composite means of table 3 by an average of 0.3 cm. Every difference is significant statistically. The relationship in early infancy is not clear; while the mean obtained by Ito[41] on 28 American Japanese neonates is 0.1 cm. higher than the composite mean for white neonates, the difference is not statistically significant.

3. Children of Mexican ancestry are smaller in head width than white children of North America. The 13 means in tables 1 and 2 for Mexican children 4 to 12 years of age average 0.3 cm. below the corresponding means in table 3 for composite samples of white children. All of the differences are significant statistically.

* Fleming's N's at successive biennial ages from 4 to 12 are 123, 339, 420, 527 and 686 for boys, and 124, 328, 486, 557 and 639 for girls.

4. Compared with the biparietal diameter of North American white children, that of North American children of Chinese descent is larger from 6 to 8 years of age and equal from 10 to 12 years of age. For each sex, the American Chinese means surpass the composite-white means by 0.2 cm. at age 6 years, and 0.1 cm. at age 8 years. These differences are significant at the 1% and 5% levels, respectively. At ages 10 and 12 years, the means from both racial groups are identical.

5. North American school children of Bohemian descent have broader heads than North American school children of Swedish descent, Italian descent, and mixed European derivation. For the age period 8 to 12 years, the means from tables 1 and 2 on children of Bohemian ancestry exceed (a) the means from tables 1 and 2 on children of Swedish ancestry by an average of 0.5 cm., (b) the means from tables 1 and 2 on children of Italian ancestry by an average of 0.4 cm., and (c) the white-composite means from table 3 by an average of 0.3 cm. In every instance the difference is statistically significant.

Variability in Head Width

The number of investigations providing statistics for variability is considerably less than the number supplying means. Moreover, a variety of methods of describing variability are used; some studies present the range, some the distance between selected percentiles, some the standard deviation, and some a combination of these measures.

TABLE 4

Head Width (cm.): Composite Measures of Variability for North American White Children. Component Samples Were Drawn from Studies Made Between 1890 and 1953

Age	Boys			Girls		
	N	Standard Deviation	Coefficient of Variability	N	Standard Deviation	Coefficient of Variability
Birth	1252	0.44	4.7	1247	0.42	4.6
3 mo.	491	0.59	5.3	457	0.53	4.9
6 mo.	632	0.60	4.9	580	0.57	4.8
1 yr.	608	0.54	4.1	554	0.52	4.1
2 yr.	509	0.55	4.1	440	0.53	4.0
4 yr.	546	0.55	3.9	550	0.49	3.6
6 yr.	774	0.53	3.7	766	0.51	3.7
8 yr.	911	0.53	3.7	830	0.50	3.5
10 yr.	900	0.53	3.6	912	0.49	3.4
12 yr.	945	0.53	3.6	799	0.51	3.5

In the synthesis of variability findings, the standard deviation is of greatest value. It is possible to utilize the separate standard deviations obtained on several similar samples and derive a standard deviation for the several samples combined.* Consequently, combined or composite standard deviations were calculated in 10 ages for North American white boys and girls. The samples pooled were as follows:

1. For boys—at birth;[4, 20, 30, 42] at 3 and 6 months;[5, 7, 23, 29, 31, 35] at 1 year;[5, 16, 23, 29, 31, 35] at 2 years;[5, 23, 29, 34, 35, 45] at 4 years;[6, 18, 23, 29, 34, 35, 45] at 6 years;[6, 14, 18, 29, 34, 35, 45, 49] at 8 and 10 years;[6, 14, 18, 26, 29, 34, 35, 45, 49] at 12 years.[4, 26, 29, 34, 35, 45, 49]

* The formula for doing this is readily accessible in another paper (Meredith[42]).

2. For girls—the same series of investigations as above, with one substitution; at each age beyond birth the study on girls by Boynton[36] replaced the complementary study for boys.[35]

Table 4 displays three composite values secured from each age-sex pooling, i.e., N, standard deviation, and coefficient of variation.* The table is read in the following manner: For a composite sample of 1,252 North American white boys at birth, the absolute variability in biparietal diameter is 0.44 cm. and the relative variability 4.7%. Besides yielding information of this order, table 4 shows:

1. Over the period from birth to 12 years of age, North American white boys are more variable in head width than North American white girls. This finding holds for both absolute variability and relative variability.

TABLE 5

HEAD WIDTH (CM.): NORMS FOR NORTH AMERICAN WHITE CHILDREN AT 6 SELECTED AGES BETWEEN BIRTH AND 10 YEARS

Age	Minimum	Percentiles:				Maximum
		10	25	75	90	
			Boys			
Birth	8.0	8.7	9.1	9.7	10.1	10.8
6 mo.	10.4	11.2	11.8	12.6	13.2	14.0
1 yr.	11.4	12.2	12.7	13.5	14.0	14.8
3 yr.	12.2	12.9	13.4	14.2	14.7	15.4
6 yr.	12.5	13.3	13.8	14.6	15.1	15.9
10 yr.	12.9	13.7	14.2	15.0	15.5	16.3
			Girls			
Birth	7.9	8.5	8.9	9.5	9.9	10.5
6 mo.	10.1	10.9	11.5	12.3	12.9	13.7
1 yr.	11.1	11.8	12.3	13.1	13.6	14.3
3 yr.	11.9	12.5	13.0	13.8	14.3	14.9
6 yr.	12.3	13.1	13.6	14.2	14.7	15.5
10 yr.	12.7	13.5	14.0	14.6	15.1	15.9

2. Absolute variability increases between birth and 6 months, decreases from 6 months to one year, and remains practically constant thereafter. For boys, the rise during the first half-year is from 0.44 cm. to 0.60 cm., and the standard deviations at 1 and 12 years are 0.54 cm. and 0.53 cm., respectively.

3. Relative variability increases from birth to 3 months, declines between 6 months and 1 year, and continues a very gradual decline throughout childhood. For girls, the rise during the first 3 months is from 4.6% to 4.9%, the decrease between 6 months and 1 year is from 4.8% to 4.1%, and the decline thereafter is to 3.5% at 12 years.

Under the assumption that head width is normally distributed in each age-sex group, the composite means and standard deviations could be used to derive percentile norms. This assumption was made, and the following normative values computed: minimum, 10th percentile, 25th percentile, 75th percentile, 90th percentile, and maximum. The results at six selected ages are listed in table 5.

There are limited quantities of empiric material that can be utilized to appraise the

* Coefficient of variation = standard deviation × 100/mean.

validity of table 5. These materials are accessible in those few studies on white children which have characterized the variability of their samples in terms of the highest and lowest records and/or the 25th and 75th percentiles.*

The highest and lowest head width measurements reported on samples of normal North American white children are close to the maximum and minimum values in table 5. The highest records for boys are 10.5 cm. at birth,[4] 13.9 cm. at 6 month,[29] 14.6 cm. at 1 year,[35] 15.6 cm. at 3 years,[16] 16.1 cm. at 6 years[35] and 16.4 cm. at 10 years;[35] the lowest records for girls are 8.2 cm. at birth,[42] 10.4 cm. at 6 months,[7] 11.4 cm. at 1 year,[36] 12.0 cm. at 3 years,[22] 12.5 cm. at 6 years[29] and 12.8 cm. at 10 years.[14] It will be seen that none of these empiric data differs more than 0.3 cm. from the table 5 values.

Twenty-fifth and 75th percentiles that are within 0.1 cm. of those listed in table 5 have been obtained from samples of both boys and girls by Tiber[8] at birth, Meredith[5] at 6 months and 1 year and Meredith[6] at 6 years. Porter,[24] on large samples of boys and girls aged 10 years, also obtained percentiles within 0.1 cm. except for one variation of 0.2 cm.

Having presented material supporting the tenability of the assumption on which table 5 was constructed, it remains to illustrate application of the table as a clinically useful frame of reference. Suppose that the following records for biparietal diameter have been secured on five North American white boys one year of age: 10.8 cm., 11.9 cm., 12.4 cm., 13.0 cm. and 13.8 cm. Table 5 shows that the first boy has an abnormally narrow head (his record falls below the lower limit of the normal range), the second boy has a narrow head (his record places him among the lowest 10% of boys his age), the third boy has a moderately narrow head, the fourth boy a head of average width, and the fifth boy a moderately wide head.

Findings from Longitudinal Data

The two previous sections have dealt with problems that can be studied from cross-sectional data, i.e., data amassed by measuring each subject at one age only. This section turns to problems which necessitate measurement of each subject at two or more ages.

Growth of Individuals: In 1896, Hall[55] published records for width of head obtained on a single infant at several ages during the first postnatal year. The subject was a normal, healthy boy of English-American lineage; his biparietal diameter, determined "with the most conscientious and painstaking exactness," was 10.0 cm. at 1 month, 11.3 cm. at 3 months, 12.5 cm. at 6 months and 13.3 cm. at 1 year. Reference to chart 1, or tables 3 and 5, shows that all of these figures are about average. Rapid decrease in growth rate during infancy is registered by the increments of 1.3 cm. for the initial two-month period, 1.2 cm. for the succeeding three month period and 0.8 cm. for the ensuing half year.

Davenport[46] presented individual growth curves for head width, covering segments of the period between 5 and 12 years, on (a) 7 feeble-minded boys, (b) 12 members of 3 family groups, (c) 2 pairs of monozygotic twins and (d) 5 physically pathologic children. For the last group, representative measurements read from the graphs are 13.3 cm. and 14.3 cm. on 2 cretins at ages 5 and 9 years, respectively, 11.1 cm. on a microcephalic child at age 11 years, 12.4 cm. on an ateliotic dwarf at age 12 years, and 13.5 cm. on an achondroplastic dwarf at age 12 years. Table 5 indicates that the head of the micro-

* The 10th and 90th percentiles are omitted from consideration because at most ages there are no studies that include these statistics.

TABLE 6

HEAD WIDTH (CM.): HIGHLY RELIABLE RECORDS ON 8 INDIVIDUALS ILLUSTRATING MINIMUM AND MAXIMUM NORMAL GAINS OVER PERIOD 5 TO 9 YEARS OF AGE

Sex	5 yr.	6 yr.	7 yr.	8 yr.	9 yr.
		Examples of 0.6 cm. increase			
Boy	15.25	15.40	15.55	15.70	15.85
Girl	14.40	14.55	14.70	14.85	15.00
Boy	14.10	14.30	14.45	14.60	14.70
Girl	13.30	13.45	13.60	13.75	13.90
		Examples of 0.2 cm. increase			
Boy	15.55	15.60	15.65	15.70	15.75
Girl	14.40	14.45	14.50	14.55	14.60
Boy	13.75	13.80	13.85	13.90	13.95
Girl	13.00	13.05	13.10	13.15	13.20

cephalic individual is more than 1.5 cm. narrower than the minimum value of the normal range.

Using an especially rigorous procedure of data collection,* Meredith[6] accumulated longitudinal material for head width on North American children of northwest European descent. From a series of protocols for 85 boys and 77 girls measured at annual intervals between 5 and 9 years of age, he selected examples to illustrate the extremes in normal increase. Table 6 presents two children of each sex representing each extreme. Inspection of the table shows that during the four year period covered:

1. Some individuals gained as much as 0.6 cm., while others gained as little as 0.2 cm.
2. Equally high and low gains occurred in individuals having wide and narrow heads, and in individuals of both sexes.

Annual and Biennial Increments: In the previously discussed investigation on North American white children by Goldstein,[18] gains in head width were secured for individuals measured at a given age and again one year later. These annual gains were distributed according to sex and age, and means obtained beginning with the age interval 3 to 4 years and continuing through 11 to 12 years. Some of the children were followed over sufficient periods of time to be included in 2 to 5 age groups. The N's and annual increment means for 7 age intervals are reproduced in the upper portion of table 7. As table 3 or chart 1 would lead one to expect, the annual gains are greater between 3 and 4 years than beyond 6 to 7 years.

The aforementioned analysis of exceptionally reliable data by Meredith[6] included study of biennial increments on the same 162 children for the periods 5 to 7 years, and 7 to 9 years. Since the data reflected no sex difference in amounts of increase, both sexes were combined. As shown in the lower portion of table 7, for each biennial period the typical gain is 0.2 cm., and the continuum of individual variation extends from 0.1 cm. to 0.3 cm.

Consistency in Rank: Meredith[6] employed a correlation approach in investigating the extent to which children maintain their positions in the group from age to age (or, stated conversely, the extent to which they move to higher or lower levels in head width dis-

* A detailed description of the procedure is given in Potter and Meredith.[43]

TABLE 7

HEAD WIDTH (CM.): ANNUAL AND BIENNIAL GAINS FOR NORTH AMERICA WHITE CHILDREN

Age Interval (yr.)	N	Mean Annual Increment	N	Mean Annual Increment
	Boys		Girls	
3– 4	33	0.17	13	0.13
4– 5	52	0.12	23	0.15
5– 6	56	0.11	33	0.12
6– 7	49	0.09	40	0.08
7– 8	33	0.08	44	0.08
9–10	22	0.07	32	0.05
11–12	16	0.08	17	0.07

	N	Mean Biennial Increment	Distribution of Increments: 0.10	0.15	0.20	0.25	0.30
		Both sexes					
5– 7	162	0.22	6	18	80	37	21
7– 9	162	0.19	12	39	76	24	11

tributions for successive ages). The relationship between biparietal diameter at 5 years of age and biparietal diameter at 9 years of age was found to be high. Specifically, $r = .98$ for 85 boys and $r = .97$ for 77 girls. These coefficients correspond closely with those obtained over approximately the same age span for stature.[64,65] It is known that the association between stature in early and late infancy is much lower;[66] whether individuals also show less constant ranking in head width during the early postnatal years than later is a problem for future study.

RELATION OF HEAD WIDTH TO OTHER VARIABLES

Relation to Other Transverse Dimensions: At one or more ages between birth and 12 years of age, there are findings on head width in relation to face width, palate width, shoulder width and hip width. The relationship between biparietal diameter and bizygomatic diameter was studied by Meredith[6] at ages 5 and 9 years. At 5 years, correlation coefficients of .54 for 85 boys and .57 for 77 girls were obtained. The r's on the same children at 9 years were .63 and .64 for boys and girls, respectively.

Bakwin and Bakwin[56] investigated the association between width of the head and width of the palate at birth. Their sample, comprising 100 white infant boys born at New York City, gave an r of .55. At ages 5 years and 7 years, Meredith and Higley[39] secured lower coefficients for biparietal diameter with "maximum horizontal distance between the buccal surfaces of the maxillary deciduous second molars."[39] The r's fell between −.04 and .26, the N's were small (28 to 36), and none of the coefficients was significant statistically.

Low positive relationships were found by Meredith[6] between width of head and width of shoulders and hips. On the same group of 85 boys at ages 5 and 9 years, the r's were .23 and .34 for biparietal diameter with biacromial diameter, .25 and .32 for biparietal diameter with bi-iliocristal diameter. Corresponding r's on the sample of 77 girls were .16, .28, .22, and .32, respectively.

Relation to Other Body Measurements: At all ages from infancy through childhood, the association between head width and head length is positive, but low. Table 8 reproduces

TABLE 8

RELATIONSHIPS BETWEEN HEAD WIDTH AND 4 OTHER BODY MEASUREMENTS

Age	Head width with head length		Head width with stature	
	N	r	N	r
		Bayley: Both sexes		
1 mo.	50	0.25	50	0.39
1 yr.	55	0.26	55	0.57
3 yr.	49	0.22	49	0.47
		Boas and Wissler: Boys		
6½ yr.	105	0.30	105	0.20
8½ yr.	121	0.14	121	0.19
10½ yr.	157	0.17	158	0.31
12½ yr.	177	0.30	177	0.24
		Boas and Wissler: Girls		
6½ yr.	84	0.30	84	0.34
8½ yr.	106	0.16	105	0.12
10½ yr.	160	0.25	160	0.18
12½ yr.	165	0.24	145	0.44
	Head width with head girth		Head width with body weight	
	N	r	N	r
		Bayley: Both sexes		
1 mo.	50	0.58	50	0.49
1 yr.	55	0.68	55	0.59
3 yr.	49	0.68	49	0.55

the coefficients obtained by Bayley[23] at infancy and preschool ages, and by Boas and Wissler[57] at older ages. The subjects of the Bayley study were white children living in or near Berkeley, Calif. Boas and Wissler utilized the data previously analyzed by West[14] on white children of Worcester, Mass.

Bakwin and Bakwin[56] studied the relationship between head width and palate length at birth, securing a correlation on 100 boys of $r = .50$. Bayley[23] investigated the association between head width and head girth in infancy and early childhood; the r's obtained are presented in the lower-left portion of table 8.

Relationships between width of head and thickness of the subcutaneous fat in selected regions of the trunk and extremities were determined by Reynolds.[58] The subjects were white children, aged 6½ years, residing in the vicinity of Yellow Springs, Ohio. Breadth of "subcutaneous tissue, plus skin" was measured on roentgenograms of the following areas: deltoid, upper forearm, chest, waist, trochanter and calf. The correlation coefficients reported for head width and the calf measurement are .27 for 62 boys, and .18 for 57 girls. Correlation of head width with the sum of the six fat measurements gave coefficients of $r = .32$ for 58 boys, and $r = .27$ for 57 girls.

Weight in relation to head width has been studied by Bayley[23] and stature in relation to head width by Bayley[23] and Boas and Wissler.[57] The findings are shown in the right half of table 8.

Additional Relationships: Bakwin and Bakwin[30] investigated the association between breadth of head and order of birth. Their mean on 812 "first-born" infants was lower than that on 841 "later-born" infants by 0.07 cm. Several studies made in Europe[67] have found a similar slight increase in neonatal head width with ascending birth order.

The association between biparietal diameter and zygotic origin was investigated by Newman et al.[59] Subjects from 8 to 18 years of age were grouped together. With age controlled statistically ("age held constant"), the head widths of 50 pairs of monozygotic twins gave a correlation coefficient of .88, and the head widths of 52 pairs of dizygotic twins a coefficient of .55. The greater likeness of monozygotic twins also was shown by an alternative method, the mean pair difference in width of head being 0.28 cm. for the monozygotic series and 0.42 cm. for the dizygotic series.

Derived measures pertaining to head width and tooth eruption were correlated by Steggerda.[60] The subjects were Michigan school children of Dutch ancestry. One series of measures represented "differences between" each child's actual head width and the mean head width for the child's age and sex. The other series represented "differences between chronologic and dental age," dental age being found by counting the number of erupted teeth present in the individual and finding the age at which the average child of like sex had this number of erupted teeth. The coefficients obtained were .06 for boys and .13 for girls.

Shuttleworth[50] studied head width during the elementary and high school years on the same children classified in several different ways. A three-category system was used. Girls were classified into early, average and late groups for (a) age of menarche, (b) age of maximum circumpuberal acceleration in stature and (c) age at which 28 permanent teeth had erupted. Boys were classified into early, average and late groups for (b) and (c). In all five instances the means for head width were slightly higher on the children in the early category than on those in the late category.

Summary

This paper brings together the research findings on biparietal diameter from more than 50 investigations. It constitutes a synthesis of present knowledge pertaining to the head breadth of physically normal, North American infants and children.

There are sections on the following topics: methodologic considerations, means for head width, variability in head width, findings from longitudinal data; and the relation of head width to other variables. Included in the section on variability is a table of norms and comments on its clinical use.

Representative generalizations are:

1. The average North American white child attains 30% of adult head width by the middle of prenatal life, 60% by birth, 80% by 6 postnatal months, 90% by 3 years and 95% by 9 years.

2. Throughout the period from birth to 12 years, the 2 sexes differ systematically: head width distributions for North American white girls have slightly lower means and smaller standard deviations than comparable distributions for boys.

3. At 1 year of age, the limits of normal variation in head width are 11.4 cm. and 14.8 cm. for North American white boys, 11.1 cm. and 14.3 cm. for North American white girls. The normal limits at age 10 years are 12.9 cm. and 16.3 cm. for boys, 12.7 cm. and 15.9 cm. for girls.

4. North American Negro school children have narrower heads than North American

white school children, and North American Japanese school children wider heads than North American white school children. The mean biparietal diameter of children of Mexican descent approximates that of American Negro children.

5. The association between width of head and length of head is low—of the order $r = .25$. A similarly low relationship exists between width of head and width of hips, but the relationship between width of head and width of face is appreciably higher.

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SPANISH ABSTRACT

Crecimiento Cefálico Durante los Primeros Doce Años de Edad

Este artículo se refiere en particular a un aspecto del tamaño cefálico: la anchura, según los datos que los autores obtuvieron de alrededor de 50 estudios publicados y no publicados.

Constituye una síntesis de los conocimientos actuales en relación a la anchura cefálica de lactantes y niños americanos físicamente normales. Las conclusiones a que se llegaron son las siguientes:

1. El niño blanco americano adquiere el 30% del tamaño cefálico del adulto a mitad de la vida prenatal, el 60% al nacer, el 80% a los seis meses de edad, el 90% a los tres años y el 95% a los nueve años.

2. Los dos sexos difieren sistematicamente del nacimiento hasta los doce años de edad en que las niñas presentan cifras promedio ligeramente menores con desviaciones standard también más pequeñas que los niños.

3. Al año de edad las desviaciones normales en la anchura cefálica de los niños son de: 11.4 a 14.8 centímetros, siendo para las niñas de 11. y 14.3 centímetros. Las medidas normales a los diez años de edad son: 12.9 a 16.3 para los niños y 12.7 a 15.9 centímetros para las niñas.

4. Mientras que los escolares negros americanos tienen la cabeza más estrecha, los escolares japoneses americanos la tienen más ancha que los escolares americanos blancos. El diámetro biparietal para niños de descendencia mexicana se aproxima al de los niños negros.

5. Hay una relación baja entre la anchura y la longitud de la cabeza, así como entre la anchura de la cabeza y la anchura de las caderas. La relación entre la anchura de la cabeza y la de la cara es un poco más alta.

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PAYMENT FOR HOSPITAL CARE OF PREMATURE INFANTS

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THE cost of various community programs designed to provide medical care for any segment of the population is of importance to public health officials, governmental fiscal officers, medical clinicians, hospital administrators and the public who are the recipients and supporters of the service either through individual direct payment or through tax funds. In the specific program designed to help give better care for the prematurely born infant in New York City premature babies weighing less than 2,000 gm. or any in "bad" condition may be transferred via a special ambulance to an "approved" premature center where the city guarantees to pay whatever the parent is unable to pay up to a certain maximum rate. The cost met from public funds for this program is therefore distributed largely to (1) operation of a special transport service; (2) payment for hospital care; (3) constructing and equipping premature centers; (4) administrative costs. The money spent by voluntary hospitals from other sources and by patients themselves is not included in this discussion.

Previous papers[1,2] have reported on the construction and equipment of premature centers and on the cost of operation of the special premature transport service in New York City.

Administrative costs of the New York City premature program are difficult to estimate. In the New York City Health Department, they include the part-time services of a medical administrator and of a pediatric consultant and the full-time services of a nursing consultant, an accountant, and one clerk, at approximately $12,000 a year. Information is not available on the administrative costs in the individual hospitals with premature centers.

There have been very few reports in the literature on the cost of payment for hospital care of premature infants in special premature centers. One analysis[3] from the Colorado Premature Center reports an average cost of approximately $439 per infant for the hospital care of 165 infants discharged alive for the year beginning July 1, 1948, based on a per diem rate of $15; the average length of stay was 29.1 days. Another study[4] from Illinois reports that "the cost of care in premature centers is about the same figure as cost of care in the local community hospital"; the per diem operating cost using the Government Reimbursable Cost Formula for 1947 or 1948 was approximately $11.00.

This report will describe the method of payment for hospital care and analyze the data on payments made for such care in the New York City premature program for the first 12 months' period the program was in operation—July 1, 1950, to July 1, 1951.

METHOD OF PAYMENT

The method developed in New York City to pay for hospital care of premature infants was based on several principles: 1. Families should pay what they can. 2. Premature

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Centers should be compensated for services they give at fair rates, or at least as near such rates as the budget officers of the city will allow. 3. "Paper work" and administrative cost should be kept at a minimum. 4. Hospitals should be paid promptly. 5. The program should interfere as little as possible with the patient's relationship to doctor and hospital.

The formula[5] to determine financial eligibility of individual families was developed* using the Federal Bureau of Labor Cost of Living statistics as applicable to New York City. Eligibility depends on three factors: (1) family income; (2) number of members in the family unit; (3) birth weight of the premature infant. From these three sets of data (usually readily available), it is relatively easy to determine the amounts to be paid by the family and by the Health Department. Decisions are made, in accord with specific instructions from the Health Department, by the staff of the hospital, either a member of the social service or the business office staff. Where decision is easily made, the Health Department accountant merely does a post-audit within the hospital after the baby has been discharged. Where a decision is difficult for the hospital to make, the data are submitted to the Health Department for review and decision shortly after the baby's admission to the premature center.

Hospital insurance plans in New York City do not cover the care of an infant within the first 90 days of life.

Payment by the Health Department is made only while the baby is cared for within the premature center, from the time of admission until the baby is discharged or until the baby reaches 2,500 gm. in weight. Payment beyond that weight level is made only for medical conditions which require extended hospitalization in the premature center.

The "paper work" consists of: (1) a financial eligibility form filled in by the hospital shortly after the baby's admission to the premature center; (2) a combined application-authorization-invoice form (the equivalent of a bill), accompanied by a medical summary, at any time after the baby has been discharged from the premature center or after the baby reaches 2,500 gm. Promptness in submitting these forms to the Health Department assures prompt payment to the hospital. There is usually no delay in the submission of these forms since the hospital wishes to be paid as quickly as possible.

This payment method[5] was worked out cooperatively with the administrative, business and social service staffs of the participating centers, and was tried out experimentally in one center before it was put into effect in all centers. It has now been in operation 3 years and has worked well.

Amount of Payment

In 1949 and 1950, when plans were being made by the Health Department to pay for hospital care of premature infants in approved premature centers, efforts were made to secure data from hospitals regarding per diem costs. At that time, very few hospitals were able to separate out the cost of care of premature infants from that of other hospital patients. A few hospitals were able to provide cost data which indicated costs to be approximately $18 per day per infant. This figure was similar to that obtained from other parts of the country. Efforts were made to secure approval of an $18 per diem rate, but the City fiscal officers allowed only a $12 per diem rate. Part family participation in pay-

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* Credit is due to Dr. Samuel M. Wishik for the development of this formula and to Miss Ethel Maslansky for the development of the income groupings.

ment is expected, wherever possible, in accord with the formula established. The hospital is at least assured of a regular payment for each case and for the most part did not complain too much at this rate. The catastrophic cost of the premature infant had often left the hospital without payment, or at least no assurance of payment.

Eligibility of Premature Centers

Standards[5] for the care of premature infants were developed by the Health Department with the assistance of the Pediatric Advisory Committee and a Nursing Subcommittee. This committee is composed of many of the leading experts in the field in New York City. Before a premature center was approved for payment, a survey of the center was

TABLE 1

Premature Infants Cared for in Approved Premature Centers in New York City—July 1, 1950, to July 1, 1951

Premature Center	No. of Premature Infants Cared for in Center 7/1/50 to 7/1/51	Premature Infants Covered by Health Department Payment 7/1/50 to 7/1/51	
		No.	%
1	266*	174	65.4
2	180	153	85.0
3	209	108	51.7
4	270	171	63.3
5	266	181	68.0
6	282	124	44.0
Total	1,473*	911	61.8

* An additional 190 infants were cared for in this center from July 1, 1950, to Dec. 1, 1950, before this center was approved.

made by the pediatric and nursing consultants of the Health Department, the survey findings presented to the Pediatric Advisory Committee, and the recommendations of the Pediatric Advisory Committee secured. All centers approved for payment reasonably met the established standards, although two centers were given conditional approval pending the initiation or completion of certain plans. Considerable guidance was given by the Pediatric Advisory Committee.

Data on the Payment Program

Number of Premature Infants: The payment program began on July 1, 1950. From this date to July 1, 1951, a total of 1,473 premature infants was cared for in the six approved premature centers. The Health Department participated in the payment for 911 infants or 61.8%. The percentage of premature infants whose payment was covered by the Health Department varied from a high of 85.0% in one voluntary hospital (Center # 2) to 44.0% in another voluntary hospital (Center # 6). (See table 1.)

Amount of Funds: A total of $291,072.00 was paid for the hospital care of 911 premature infants while in the six approved premature centers, or an average of $319.51 per infant. The average amount paid per infant varied from a high of $419.22 in one

voluntary hospital center (Center # 4) to a low of $218.25 in one municipal hospital center (Center # 5). (See table 2.)

Of the total of $291,072.00, family payments amounted to $8,348.53, or 2.9% of the total funds expended. The percentage of total funds paid by parents ranged from zero in one municipal hospital center (Center # 1) to 4.4% in one voluntary hospital center (Center # 6). Of the 911 babies, the parents participated in the payment for 108 (11.9%). The percentage of babies with parental participation in payment varied from zero in one municipal hospital center (Center # 1) to 24.0% in one voluntary hospital center (Center # 4). (See table 2.) The municipal hospital drew its clientele from lower economic groups.

TABLE 2

AMOUNT OF FUNDS EXPENDED FOR HOSPITAL CARE OF PREMATURE INFANTS IN NEW YORK CITY—JULY 1, 1950, TO JULY 1, 1951

Premature Center	Total Payments	Total No. of Babies	Average Payment Per Baby	Parent Payments			
				Babies		Funds	
				No.	% of Total	Amount	% of Total
1	$ 44,172.00	174	$253.86	—	—	—	—
2	51,648.00	153	337.57	26	17.0	$2,257.50	4.4
3	43,956.00	108	407.00	15	13.9	1,431.16	3.3
4	71,688.00	171	419.23	41	24.0	2,840.00	4.0
5	39,504.00	181	218.25	1	0.6	30.00	0.18
6	40,104.00	124	323.42	25	20.2	1,789.87	4.5
Total	$291,072.00	911	$319.51	108	11.9	$8,348.53	2.9

Of the $282,723.47 expended by the New York City Department of Health, $145,536.95 (51%) was expended for the care of 562 intramural infants, and $137,186.52 (49%) for the care of 349 transported infants. The average of city payment for the intramural infants was $259; for the transported group, $393. Centers # 3 and # 4, in voluntary hospitals, were reimbursed proportionately much more for the care of extramural infants (67% and 75%, respectively) than the four other centers. These differences are a reflection of the percentages of extramural infants and number of premature center days' care in these two centers. (See table 3.) Center # 1, a large center in a municipal hospital with a large maternity section, provided the lowest proportion of service for the extramural group.

Length of Stay: A total of 24,256 hospital days in the premature centers was paid for this group of 911 premature infants, or an average of 26.6 days per infant. This average is comparable to previous reports.[6] The average length of stay ranged from a high of 34.9 days in Center # 4 to a low of 18.2 days in Center # 5. (See table 4.) The three centers having the longest average length of stay (Centers # 4, # 3 and # 2) were the centers to which the smallest premature infants were usually transported. It would therefore be expected that these centers would have cared for the highest percentage of babies in the lower weight groups. While this is true of Centers # 3 and

TABLE 3

PERCENTAGE OF PREMATURE INFANTS, PREMATURE CENTER DAYS AND FUNDS EXPENDED BY CITY PREMATURE PAYMENT PROGRAM, BY PREMATURE CENTER AND BY PLACE OF BIRTH

Premature Center	Premature Infants Care for				No. of Days' Care				Funds Expended by the City Health Department				
									Intramural		Extramural		
	Total	Extramural	Intramural	% Extramural	Total	Extramural	Intramural	% Extramural	Payment	Average Per Case	Payment	Average Per Case	% Extramural
1	174	33	141	19	3,681	936	2,745	25	$ 32,940.00	$234	$ 11,232.00	$340	25
2	153	41	112	27	4,304	1,470	2,834	34	32,203.50	288	17,187.00	419	35
3	108	70	38	65	3,663	2,469	1,194	67	14,289.00	376	28,235.84	403	65
4	171	116	55	68	5,974	4,510	1,464	75	16,660.00	303	52,188.00	450	76
5	181	46	135	25	3,292	991	2,301	30	27,612.00	205	11,862.00	258	30
6	124	43	81	35	3,342	1,406	1,936	42	21,832.45	270	16,481.68	383	43
Total	911	349	562	38	24,256	11,782	12,474	49	$145,336.95	259	$137,186.52	$393	49

2, it is not true of Center # 4. There must therefore be another explanation for the long period of center care in Center # 4. (See table 5.)

Of the average length of stay of 26.6 days, an average of only 0.8 days was spent for babies who required care in the centers after they had attained a weight of 2,500 gm. One hundred twenty-one babies (13.3%) stayed in a premature center after they reached 2,500 gm.; the percentage varied from 8.2% in one center to 24.2% in another center. Seven hundred fifty-two days of center care were expended after the babies reached 2,500 gm., or 3.1% of the total days' care. The highest number of days' care spent by babies beyond 2,500 gm. was 263 (7.2%) in Center # 3 which was carrying on considerable research on retrolental fibroplasia. (Table 4.)

The average age at death of the entire group was 7.4 days; the average age at death ranged from 3.3 days in Center # 2 to 19.0 days in Center # 4. Two centers, # 3 and # 4, had a much older average age at death than the others. These same two centers had an older average age at discharge home and at discharge to other services

TABLE 4

AVERAGE LENGTH OF STAY IN PREMATURE CENTERS IN NEW YORK CITY JULY 1, 1950, TO JULY 1, 1951

Premature Center	Total No. of Infants	Cases over 2500 gm.		Days Care						Per Cent of Total Days Care Spent After Baby Reached 2500 gm.
				Total		Up to 2500 gm.		Over 2500 gm.		
		No.	% of Total	No.	Average	No.	Average	No.	Average	
1	174	18	10.3	3,681	21.2	3,634	20.9	47	0.3	1.3
2	153	13	8.5	4,304	28.1	4,184	27.3	120	0.8	2.8
3	108	25	23.1	3,663	33.9	3,400	31.5	263	2.4	7.2
4	171	14	8.2	5,974	34.9	5,905	34.5	69	0.4	1.2
5	181	21	11.6	3,292	18.2	3,142	17.4	150	0.8	4.6
6	124	30	24.2	3,342	27.0	3,239	26.1	103	0.8	3.1
Total	911	121	13.3	24,256	26.6	23,504	25.8	752	0.8	3.1

TABLE 5

BIRTH WEIGHT DISTRIBUTION OF BABIES CARED FOR IN PREMATURE CENTERS IN NEW YORK CITY—JULY 1, 1950, TO JULY 1, 1951

Premature Center	Total No. Babies	1000 gm. or Less		1001–1500 gm.		1501–2000 gm.		2001–2500 gm.		Per Cent of Total Under 1501 gm.
		No.	%	No.	%	No.	%	No.	%	
1	174	33	19.0	27	15.5	54	31.0	60	34.5	34.5
2	153	13	8.5	37	24.2	45	29.4	58	37.9	32.7
3	108	23	21.3	39	36.1	37	34.3	9	8.8	57.4
4	171	11	6.4	28	16.4	93	54.4	39	22.8	22.8
5	181	14	7.7	24	13.3	65	35.9	78	43.1	21.0
6	124	11	8.9	18	14.5	34	27.4	61	49.2	23.4
Total	911	105	11.5	173	19.0	328	36.0	305	33.5	30.5

TABLE 6

AGE OF DEATH, DISCHARGE HOME AND DISCHARGE TO OTHER SERVICE BY TYPE OF DISCHARGE OF PREMATURE INFANTS WHOSE CARE WAS PAID FOR BY PREMATURE PROGRAM

Premature Center	Age at Death (days)	Age at Discharge Home (days)	Age at Discharge to Other Service (days)
1	5.7	32.2	30.3
2	3.3	33.1	42.6
3	13.4	46.3	56.2
4	19.0	40.6	44.7
5	4.2	24.5	24.3
6	6.2	35.1	—
Total	7.4	34.8	35.6

TABLE 7

AVERAGE LENGTH OF TIME IN DAYS TO REACH 2500 GM. OR TO BE DISCHARGED ALIVE AT WEIGHT 2251–2500 GM., OF INFANTS BORN IN HOSPITAL OF CARE: BY CENTER AND BIRTH WEIGHT

Premature Center	Birth Weight											
	1000 gm. or Less			1001–1500 gm.			1501–2000 gm.			2001–2500 gm.		
	Days	Infants	Average	Days	Infants	Average	Days	Infants	Average	Days	Infants	Average
1	—	—	—	484	8	61	1,121	34	33	1,133	53	21
2	144	2	72	722	12	60	1,050	32	33	908	54	17
3	—	—	—	418	8	52	451	15	30	111	4	28
4	72	1	72	197	3	66	833	23	36	409	26	16
5	—	—	—	317	7	45	922	37	25	977	61	16
6	94	1	94	203	3	68	568	12	47	1,034	52	20
Total	310	4	78	2,341	41	57	4,945	153	32	4,572	250	18

within the hospital. These findings cannot be explained at the present time. (See table 6.)

Another question relating to length of stay is, "Did some centers take a longer time for their infants to reach a safe weight for discharge than other centers?" Table 7 presents the available data. In the three larger weight groups (1,000 gm. and over) where the numbers are large enough to be statistically significant, the averages were 57 days in the 1,001 to 1,500 gm. group, 32 days in the 1,501 to 2,000 gm. group, and 18 days in the 2,001 to 2,500 gm. group. The significant findings are: (1) Center # 5 took a shorter time in the 1,001 to 1,500 gm. group; (2) Center # 6 took a longer time in the 1,501 to 2,000 gm. group; (3) Center # 3 took a longer time in the 2,001 to 2,500 gm. group. These data were further analyzed by color, and no significant differences were found between the white and nonwhite groups.

Age and Type of Transport to Premature Centers: Of the 911 babies cared for in premature centers, 562 (61.7%) were born in the institution of which the premature

TABLE 8

AGE AT TRANSPORT OF PREMATURE INFANTS

Age at Transport	No. of Infants	% of Total
Under 1 day	116	33.3
1 day	83	23.6
2 days	21	6.0
3 days	20	5.7
4 days	11	3.2
5 days	12	3.4
6 days	3	0.9
7 days	8	2.3
8 days	2	0.6
9 days and over	35	10.1
Unknown	38	10.9
Total	349	100.0

center is a part; 325 (35.7%) were brought to the premature centers by the special transport ambulance service provided by the City Departments of Health and Hospitals; and 19 (2.1%) were brought to the centers by other ambulances. Of the 349 infants in the entire transport group only 325 (93.1%) were transported by the special ambulance service.

The age at transport of the extramural (transport) group is shown in table 8. One-third of the infants were transported when they were less than 1 day of age, and another quarter of the infants when they were 1 day of age. Eleven per cent were moved after the first week of life. This last group is disproportionately large. Delay in transport was usually due to the lack of a vacancy in a premature center, or the fact that the hospital of birth for financial reasons did not wish to transfer the baby until the mother was discharged home.

Mortality: In comparing the hospital mortality percentages of the intramural group with the group transported by the special premature ambulance, table 9 shows that the latter group had a lower mortality in all weight groups except the 2,001 and 2,500 gm. group. The explanation for the higher hospital mortality in the 2,001 to 2,500 gm. group

TABLE 9

HOSPITAL MORTALITY PERCENTAGE OF INTRAMURAL GROUP AND GROUP TRANSPORTED BY SPECIAL PREMATURE AMBULANCE, BY AGE AT TRANSPORT AND BY WEIGHT GROUP

Wt. Group (gm.)	Intramural Group			Group Transported By Special Premature Ambulance																				
				Total Group			Group Transported under 1 Day of Age			Group Transported at 1 Day of Age			Group Transported at 2 Days of Age			Group Transported at 3 Days of Age			Group Transported at Over 3 Days of Age			Age at Transport Unknown		
	No. Born	No. Died	Mort. %	No.	No. Died	Mort. %	No.	No. Died	Mort. %	No.	No. Died	Mort. %	No.	No. Died	Mort. %	No.	No. Died	Mort. %	No.	No. Died	Mort. %	No.	No. Died	Mort. %
1000 or less	51	47	92.2	50	28	56.0	25	18	72.0	15	9	60.0	2	—	—	—	—	—	1	—	—	7	1	14.3
1001–1500	62	19	30.6	108	26	24.1	43	19	44.2	26	5	19.2	6	2	33.3	6	—	—	9	—	—	18	—	—
1501–2000	187	27	14.4	135	10	7.4	24	4	16.7	34	1	2.9	11	1	9.1	10	—	—	46	4	8.7	10	—	—
2001–2500	263	7	2.7	31	2	6.5	5	—	—	7	1	14.3	1	—	—	4	—	—	14	1	7.1	—	—	—
Total	563	100	17.8	324	66	20.4	97	41	42.3	82	16	19.5	20	3	15	20	—	—	70	5	7.1	35	1	2.9

of the extramural series is that, by and large, request for transport for this group was made only when these larger babies exhibited signs or symptoms of some abnormality. It should be remembered that priority in transport was given to: (1) the smallest babies; (2) babies in poor condition; (3) babies born at home; (4) babies born in hospitals least well equipped and staffed to care for them.

That age at transport may be a factor in the baby's ability to survive is also shown in table 9. It is possible that the best plan might be to have each maternity hospital well staffed and equipped to give good and safe emergency care at the place of birth and then to transport the infant after the first 24 hours of life. Such a plan would mean that each maternity hospital should have the following provided at all times: an incubator and

TABLE 10

TRANSFERRED TO OTHER HOSPITAL SERVICES BY REASON AND BY INSTITUTION OF CARE JULY, 1950, TO JUNE, 1951

Premature Center	Total	Not Transferred	Reason Transferred						
			Total	Acute Disease	Surgical	Other Medical	No Space	Social	Other
1	174	150	24	—	—	—	3	21	—
2	153	137	16	4	1	4	1	6	—
3	108	96	12	—	1	1	—	10	—
4	171	158	13	—	1	—	—	11	1
5	181	151	30	5	—	1	8	15	1
6	124	124	—	—	—	—	—	—	—
Total	911	816	95	9	3	6	12	63	2

oxygen in each delivery room and in each nursery; a nurse who has had special training in the care of premature infants; emergency standing orders; and a pediatrician to see each premature infant. Such a situation does not obtain in New York City at present.[7]

An effort was made to do some comparisons between (1) individual hospitals in the intramural and extramural series; (2) color in the intramural and extramural series. No conclusions can be drawn in these analyses because the numbers are too small for comparison.

Transfer from Premature Centers to Other Hospital Services: Of the 911 infants, 95 (10.4%) were transferred to other services within the hospital. These babies were transferred to either the pediatric service or to the regular nursery service for full-term newborn infants, depending on the individual hospital policy and condition of the infant. The reasons for such transfer are shown in table 10. "Social" reasons accounted for two-thirds of this group; the next largest group was transferred because the available space was needed for smaller prematures; small percentages were transferred because of acute disease, other medical problems and surgical conditions. Of the three hospitals with the highest percentages of transfer for "social" reasons, two were of the municipal type, showing the close correlation with economic status.

Retention of Babies Beyond 2,500 gm. in Centers: Of the 911 babies, 121 (13.3%) were kept beyond 2,500 gm. Of this group approximately one-quarter of the babies were kept for reasons of acute disease, one-quarter for "other medical" reasons and almost one-half for "other" reasons. (See table 11.) In two hospitals (Centers # 3 and # 6)

TABLE 11

PREMATURE INFANTS KEPT BEYOND 2500 GM. BY REASON AND BY INSTITUTION
NEW YORK CITY—JULY 1, 1950, TO JULY 1, 1951

Premature Center	Total Infants	Not Kept	Reason Kept Beyond 2500 gm.											
			Total		Acute Disease		Surgical		Other Medical		Still Immature		Other	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1	174	156	18	10.3	1	0.6	—	—	—	—	—	—	17	9.8
2	153	140	13	8.5	6	3.9	—	—	5	3.3	—	—	2	1.3
3	108	83	25	23.1	9	8.3	1	0.9	6	5.6	1	0.9	8	7.4
4	171	157	14	8.2	5	2.9	1	0.6	—	—	1	0.6	7	4.1
5	181	160	21	11.6	4	2.2	1	0.6	10	5.5	—	—	6	3.3
6	124	94	30	24.2	4	3.2	3	2.4	9	7.3	—	—	14	11.3
Total	911	790	121	13.3	29	3.2	6	0.7	30	3.3	2	0.2	54	5.9

almost one-quarter of all babies in the center were kept beyond 2,500 gm. in weight; in these two hospitals the reasons were widely distributed, although nonmedical and nonsurgical reasons played a large rôle in both centers.

A total of 54 babies were kept beyond 2,500 gm. in premature centers for "other reasons." These reasons are stated in table 12, with the number of days spent. A careful scrutiny reveals that practically all of them fall into the "social" category. A few are related to the hospital policy of weighing or to delay in discharge. A total of 131 days was used for this group of 54 babies; this represents an expenditure of $1,572, of which only $40 was paid by parents.

DISCUSSION

In developing a community program for prematurely born infants, the question of including payments for those infants for whom good care might not otherwise be avail-

TABLE 12

PREMATURE BABIES KEPT BEYOND 2500 GM. FOR "OTHER REASONS"

Reason	No. Babies	No. Hospital Days
Home Not Ready	22	57
Hospital Delay in Discharging Baby	7	10
Parents Delayed in Coming for Child	6	12
Awaiting Placement by Department of Welfare	5	32
Parents Not Located at Once	2	3
Parents Wanted to Take Twins Home Together	2	2
Infrequent Weighing Policy by Hospital	2	2
Miscellaneous*	4	8
Unknown	4	5
	54	131

* Includes bad weather (1), illness of mother (1), fluctuation of baby's weight (1) and delay in receiving home report (1).

able will undoubtedly arise. In discussions with hospitals, the guarantee of payment for hospital care was a "must," before the hospitals found it possible to plan premature centers. This, of course, is related to the high cost of the specialized care necessary. Payment of hospital care, therefore, is in the authors' opinion an important part of any program which tries to solve the community total problem. Ideally this payment program should be based upon the true cost of care. It would be helpful if administrators of hospitals operating premature centers would separate the costs of care of premature infants in their centers from the costs of other hospital patients.

Another early basic decision is whether the payment program should include both extradural and intramural infants, as in the New York City program, or whether it should cover extramural infants only as in some other programs. The disadvantage of including both extramural and intramural infants is the higher cost to the community from tax funds, and it might be argued that any community hospital accepting maternity and newborn patients has a community responsibility for those patients which it does accept. The disadvantage of including only extramural infants in the payment program is a very practical one—in discussions with hospitals, the hospitals made it clear that they would only be able to develop premature centers if financial subsidy were made available for all premature infants cared for within the center whose families were unable to pay. In New York City, the question was therefore decided on this practical basis. Payment had to include both groups of infants if centers were to be developed.

In planning premature centers with the individual hospitals, the question arises as to the proportion of total infants cared for within the centers which should be derived from the extramural group. Thirty-eight per cent of the babies whose care was paid for by the City payment program were of the extramural group. Is this over-all percentage a fair one, or should it be higher? Furthermore, when the individual centers are studied, the proportion of extramural infants varies from 19% to 68%. With the long list of babies awaiting placement daily, it might be reasonable to plan with the hospitals what the proportion of extramural infants should be, so that the requests for transport to premature centers might be met more promptly and adequately. In reviewing the data, it would seem that some of the hospitals might find it necessary either to provide larger centers, or to restrict their intramural admissions to the centers to babies weighing less than 2,000 gm. at birth and to those larger babies with special problems. The latter policy would seem to be the more desirable one, if highly specialized care is to be directed to those babies who need it most. A concomitant activity would be to raise the level of care in the full-term nurseries of hospitals having premature centers to the point where the majority of the larger premature infants could be safely cared for there. This activity of the Health Department accompanied and actually preceded that of the development of the special services for premature infants, through its hospital consultation program.

The fact that 54 infants (6%) with a total of 131 center days were kept in the premature centers beyond 2,500 gm. for nonmedical reasons is important; $1,572 or 17% of the payment for babies beyond 2,500 gm. was expended for this group. In this era of mounting hospital costs, this becomes an important community problem. The American Hospital Association recommends that every hospital examine and appraise its own method of operation so that unnecessary hospitalization may be reduced and eliminated.[8] In the case of the premature infant the following steps seem necessary and feasible if unnecessary hospitalization is to be eliminated: (1) discharge decision to be anticipated before the infant reaches 2,500 gm.; (2) close relationship with the parents of premature in-

fants so that they will be psychologically ready to take their babies home promptly, when the babies are medically ready; (3) close relationship with the community public health nursing agencies, so that the home may be prepared to receive the infant as soon as he is medically ready for discharge; (4) strengthening of social and child welfare services in the community for those children who for social or medical reasons will never be able to go to their own home.

The question of the "best" time to transport prematurely born infants to centers cannot be answered at this time. Emphasis should be placed on providing safe immediate care of the infant at the hospital of birth. When that objective has been reached, it may be desirable to delay the transfer of hospital-born premature infants until they have reached 24 hours of age. It is not anticipated, however, that this modification of policy would apply to the care of the home-born premature infant.

Summary

This report describes the method developed by the New York City Department of Health to pay for the hospital care of prematurely born infants in six approved premature centers. It also discusses the results of this payment program. A total of $291,072.00 was paid for the care of 911 infants in a one-year period, of whom 38% were extramural infants. Family payment amounted to only 2.9% of the total funds expended. The average length of center stay was 26.6 days. Variations between centers were noted in the length of time it took the infants to reach their discharge weight of 2,500 gm. Thirteen per cent of the infants were kept in the centers after they reached 2,500 gm. in weight, approximately one-half of whom were for nonmedical reasons. Some of the implications of the program for public health and hospital administrators, pediatricians and social workers are discussed.

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Spanish Abstract

Pago de la Atención Hospitalaria a Niños Prematuros

En este informe se describe el sistema que sigue el Departamento de Salud de la ciudad de Nueva York en el pago de la atención hospitalaria para los prematuros distribuídos en sus 6 centros aprobados, y se analizan los ingresos obtenidos por tal atención durante el período de julio lo. de 1950 a julio de 1951. El costo del programa comprende los gastos por: servicio de transporte, atención hospitalaria, construcción y equipo de los centros para prematuros y servicios administrativos. El programa a su vez se basa en los siguientes principios: cuotas fijadas de acuerdo con las posi-

bilidades familiares, compensación al centro de prematuros por los servicios que proporciona por cuotas módicas, servicios administrativos a sus mínimas cifras, pago rápido de las cuotas y escasa interferencia en las relaciones del paciente con el médico y el hospital.

La investigación del Departamento de Salud en centros ajenos a él y en diversos sitios de la Unión Americana, durante los años de 1949 y 1950, señala la cifra de 18 dólares como el costo por día y por niño. En el estudio de este programa particular, el Departamento de Salud calcula haber gastado para el período de 1950-1951, la cantidad de 291,072 dólares para un total de 911 niños; 562 "niños intrahospitalarios" consumiendo el 51% y 349 niños traídos a los centros, el 49%. El promedio de estancia por niño fue de 26.6 días. El costo promedio para los primeros fue de 259 dólares y para los segundos de 393 dólares. La restitución familiar fue de sólo 2.9%. El promedio de estancia para los niños que fallecieron fue de 7.4 días.

Se observó que el grupo de niños traídos de fuera hacia los centros tuvo mortalidad más baja que los correspondientes del mismo peso llamado "intrahospitalarios," excepto en el de los niños de 2001 a 2500 gramos. Esto se explica por el hecho de que se solicitó la atención hospitalaria sólo para aquellos niños del peso señalado que presentaban signos y síntomas anormales (prioridad en el transporte se dió siempre a los niños más pequeños, a los niños en malas condiciones, a los niños que nacieron a domicilio y a los niños que nacieron en hospitales más pobremente equipados y con menor calidad de personal técnico).

Los autores concluyen que todo programa que la comunidad desarrolle para atender a niños prematuros, debe incluir los gastos de aquéllos sin capacidad económica para recibir buena atención; esta atención tan especializada requiere inevitablemente costos elevados. Los administradores de hospitales que manejan niños prematuros deben separar los gastos en el manejo de estos niños de los de otros pacientes. Otro punto de interés se refiere a reducir la atención sólo a los niños nacidos en el hospital particular o bien aceptar a los que sean transportados de otros centros hospitalarios, de su domicilio, etc. (niños de "extramuros").

Se destacan en el presente trabajo otros problemas en relación a los niños atendidos durante el período señalado.

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Pediatrics

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SPECIAL SECTIONS

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

VITAL STATISTICS—1952

THE annual summary charts of essential vital statistics in the U.S.A., based on preliminary estimates, are reprinted below from the Monthly Vital Statistics Report, National Office of Vital Statistics, Public Health Service, U. S. Department of Health, Education and Welfare. They show, in general, little change from the preceding year, although, in some instances, monthly variations are greater.

Pediatricians turn first to infant mortality as a sensitive index of pediatric and public health progress. Although the total number of infant deaths has increased to 109,000, the rate is essentially unchanged—28.6. Preliminary over-all figures, however, do not show the important variations in mortality by race, by specific age periods of the first year of life or by the chief causes, factors which need to be analyzed in order to interpret infant mortality rates properly. One interesting breakdown is available—that by state and geographic region, presented in the table.

Far less variation is apparent than was true 25 years ago. Only three states—New Mexico, Arizona and South Carolina—have rates over 40, yet in 1936, at the beginning of the most recent generalized national and statewide effort for promotion of child health and prevention of infant mortality, the rates in these states ranged around 100 or more. There is ample room for pride in these accomplishments but this does not diminish the opportunity and necessity for further reduction in needless deaths.

Births continue at a high level with another new all-time record of total births, 3,824,000. This figure exceeds the previous maximum (1951) of 3,758,000, which was in turn higher than the 1947 peak of 3,699,940. Since there are still a number of births for which no birth certificates are filed, it is necessary to correct the figures for under-reporting if one is to estimate more closely the increase in the country's population. On this basis the total births in 1951 and 1952 are assumed to be 3,833,000 and

TABLE 1

PROVISIONAL INFANT DEATH RATES
REPORTING AREA, EACH DIVISION, AND STATE, 1951 AND 1952

AREA	INFANT DEATH RATES (per 1000 live births)	
	1952	1951
TOTAL: 46 STATES AND DISTRICT OF COLUMBIA	28.6	28.7
NEW ENGLAND	22.7	23.9
Maine	27.4	28.3
New Hampshire	22.9	23.2
Vermont	23.8	27.7
Massachusetts	—	—
Rhode Island	21.2	23.8
Connecticut	20.8	21.1
MIDDLE ATLANTIC	24.6	24.2
New York	24.2	23.6
New Jersey	23.4	23.9
Pennsylvania	25.8	25.1
EAST NORTH CENTRAL	25.3	25.1
Ohio	24.5	23.6
Indiana	26.5	26.7
Illinois	25.3	25.3
Michigan	26.6	25.9
Wisconsin	23.8	24.7
WEST NORTH CENTRAL	24.8	24.7
Minnesota	23.0	23.9
Iowa	23.6	24.6
Missouri	27.6	26.7
North Dakota	25.0	26.4
South Dakota	25.4	23.1
Nebraska	22.4	22.0
Kansas	25.2	24.3
SOUTH ATLANTIC	34.1	32.9
Delaware	27.9	27.4
Maryland	29.4	28.6
District of Columbia	29.0	25.9
Virginia	35.5	35.5
West Virginia	34.5	32.4
North Carolina	34.8	32.9
South Carolina	40.9	36.2
Georgia	32.5	34.3
Florida	34.4	32.8
EAST SOUTH CENTRAL	35.8	35.0
Kentucky	34.3	31.9
Tennessee	33.7	35.3
Alabama	36.7	36.8
Mississippi	39.3	35.8

TABLE 1—*Continued*

Area	Infant Death Rates (per 1000 live births)	
	1952	1951
West South Central	32.2	25.0
Arkansas	26.5	25.3
Louisiana	32.7	33.5
Oklahoma	29.0	30.0
Texas	33.7	38.7
Mountain	33.7	36.4
Montana	27.1	27.1
Idaho	24.7	25.0
Wyoming	29.5	29.1
Colorado	32.0	33.2
New Mexico	46.4	57.2
Arizona	44.1	50.4
Utah	24.3	24.1
Nevada	36.2	35.1
Pacific	24.0	23.8
Washington	23.8	23.9
Oregon	24.3	23.8
California	(24.9)	(24.3)

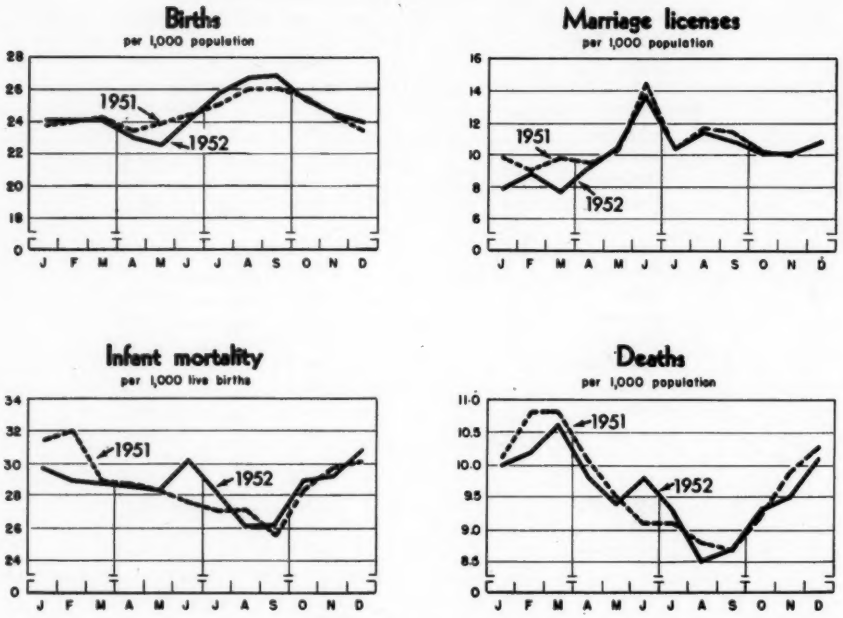
3,889,000, respectively. For the seven years since the war, 1946-52, registration totaled 25,219,358 but there are estimated to be approximately 650,000 more actual births in that period which were not registered.

Preliminary estimates of birth order, based on experience in several states, indicates that the 1951 increase in births was mainly in 1st, 3rd, and 4th births—increases of 5, 9 and 13%, respectively. Increase in first births presumably followed the increase in marriages in 1950 related to the Korea outbreak. Since marriages were fewer in 1951 the increase in births in 1952 is more likely in the higher birth orders than in first births.

The birth rate in 1952, based on registered births, was approximately 24.6 per 1000 population, showing little change from 1951. Both rates are slightly lower than the high point reached in 1947 but are substantially higher than the rates in the early 1940's. It is difficult to predict how long these relatively high birth rates will continue but it is well to note that they are still considerably less than, for example, the rates of 40 or more found in many other countries in this hemisphere.

The estimated number of deaths registered in 1952 was 1,494,000, representing a rate of 9.6 per 1000 population. For the past four years the rates have varied little from this generally low level. The difference between births and deaths, of course, represents the "natural" increase in population, estimated therefore to be almost 2,400,000 in 1952. The Department of Commerce maintains a constant population estimate, based not only on births and deaths but also immigration and emigration. Early in August 1953 the population of the U.S.A. was thought to have passed 160,000,000. Many factors are responsible for our recent rapid growth and a considerable portion is related to longer

Provisional Vital Statistics for the United States



life expectancy as death rates among older persons continue to decrease. Nevertheless, as Dr. Martha Eliot pointed out recently, the relatively high birth rate and relatively low infant death rate have particular significance for pediatricians and mean that "we are growing younger faster than we are growing older."

SPECIAL REVIEWS

JOSEPH STOKES, JR., M.D., *Editor*

DERMATOMYOSITIS

Report of 26 Cases in Children with a Discussion of Endocrine Therapy in 13

By RALPH J. P. WEDGWOOD, M.D., CHARLES D. COOK, M.D., AND JONATHAN COHEN, M.D.
Boston

THE purpose of this report is to present 26 cases of dermatomyositis in children in order to show the natural course of the disease and to evaluate endocrine therapy with testosterone, adrenocorticotropic hormone and cortisone.

The patients in this report represent all the children in whom the diagnosis could be substantiated at the Children's Medical Center between 1916 and 1952 and one case seen at the Massachusetts General Hospital.

HISTORICAL REVIEW

Dermatomyositis is a generalized disease occasionally involving many organs of the body but characterized primarily by nonsuppurative inflammation of the striated musculature, usually accompanied by cutaneous lesions. In rare cases the cutaneous lesions are absent in which case the disease should be more properly termed polymyositis. Wagner,[1] Hepp[2] and Unverricht[3] independently described the disease for the first time in 1887, and Unverricht attached the name "dermatomyositis" to the syndrome several years later. Many individual case reports and small series have appeared in the literature since the disease was first described. In reviews of the literature, Karelitz and Welt[4] were able to collect 75 cases in 1932, 22 of which had occurred in children, Schuermann[5] found 263 cases in 1939 of which 47 were children under the age of 15 years and in 1950, Selander[6] collected 22 cases in children under 7 years of age.

Many theories of the etiology of dermatomyositis have been proposed but so far none has been substantiated. Bacterial, parasitic or viral agents have been suggested repeatedly but there has been no convincing evidence presented. Occasionally tissue cultures have been positive for staphylococci or streptococci[7,8] but the evidence for these as etiologic factors is not convincing and, although Clark[9] felt that one of his cases responded to penicillin, this has not been substantiated by other observers. Superficial similarities between this disease and nutritional disturbances in man and experimental animals have suggested relationships which do not seem warranted on the basis of therapeutic trials with the supposedly implicated factors. Langmead[10] suggested that dermatomyositis belonged to a group of diseases including scleroderma, sclerodactyly, myositis fibrosa and calcinosis universalis. The disease appears to be one of the group of so-called "collagen" diseases[11] and the skin and muscle lesions perhaps are related to some undefined form of immunologic reaction.

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Clinical Material (Table 1, Chart 1)

The 26 cases of generalized dermatomyositis included in this report occurred in children between the ages of 2 and 11 years. Pathologic findings were consistent with the diagnosis in all the 23 children from whom a biopsy was obtained. Eleven children were male and 15 female. One child (Case 25) was Negro. Sixteen of the 26 are alive and have been seen or heard from in detail at the time of writing. All have been followed at least one year from the onset of the disease, and 10 of the 16 living patients have had their disease for 3 or more years. One child (Case 3) was followed 9, another (Case 10) 14 and another (Case 19) 19 years from the onset of the disease. Four of the children (Cases 1, 14, 20 and 22) are still felt to have active disease; 4 (Cases 9, 11, 12 and 13) have severely crippling residual contractures. The other 8 children, while showing residual evidence of the disease (calcinosis, localized muscle atrophy, minor contractures or minimal skin changes) are able to lead normal active lives.

Eight of the 10 children who died succumbed between 4 and 26 mo. after the onset of symptoms, suggesting that the disease process usually becomes inactive after this period.

Two children (Cases 4 and 6) were mirror-image twins. The disease in one of these girls began one year before the onset in her twin. The child who developed the disease first had minimal involvement, while the second sibling had a more severe form of the disease with resultant minor limitation of motion. In both of these cases the findings in biopsy were characteristic.

A prominent feature of dermatomyositis is the insidious onset. Most of the children had the disease for weeks before medical advice was sought. However, occasionally the

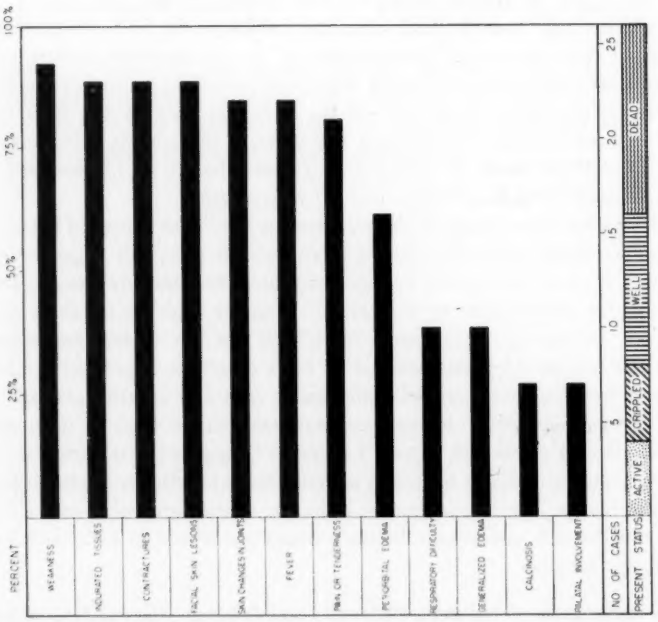

Chart 1. Graphic representation of findings on 26 children with dermatomyositis.

TABLE 1

CLINICAL DATA ON 26 CHILDREN WITH DERMATOMYOSITIS

Case No.	Age at Onset	Sex	Weakness	Indurated Tissues	Facial Skin Lesions	Skin Changes Over Joints	Contractures	Pain or Tenderness	Fever	Periorbital Edema	Respiratory Difficulty	Generalized Edema	Palatal Involvement	Calcinosis	Present Status	Duration from Onset to Present or Death	Age at Present or at Death	Cause of Death
1	2 3/12	M	+	+	0	0	+	+	+	0	0	+	0	0	Active	5 9/12	7 3/12	
2	3 2/12	M	+	+	+	+	+	0	0	+	+	+	+	0	Dead	9/12	3 11/12	Palato-respiratory
3	3 3/12	F	+	0	+	+	0	0	0	0	0	0	0	+	Well	8 10/12	12 5/12	
4	4 0/12	F	+	+	0	+	0	+	+	0	0	0	0	0	Well	3 0/12	7 0/12	
5	4 8/12	F	0	+	+	0	+	+	0	+	?	0	?	+	Dead	1 10/12	6 4/12	Pneumonia
6	5 0/12	F	0	+	+	+	+	0	+	0	+	0	0	0	Well	2 0/12	7 0/12	
7	5 0/12	M	+	+	+	+	+	+	+	+	0	0	+	0	Dead	1 9/12	6 9/12	Paba toxicity
8	5 10/12	F	+	+	+	+	+	+	+	+	+	0	+	0	Dead	1 12/12	7 8/12	Palato-respiratory
9	6 1/12	F	+	+	+	+	+	+	+	0	0	0	0	0	Crippled	3 4/12	9 1/12	
10	6 8/12	M	+	+	+	+	+	0	+	+	0	0	0	+	Well	13 9/12	20 5/12	
11	6 8/12	F	+	+	+	+	+	+	+	+	0	+	0	?	Crippled	5 9/12	12 5/12	
12	6 8/12	F	+	+	+	+	+	+	+	0	0	0	0	0	Crippled	7 3/12	14 2/12	
13	7 0/12	F	+	+	+	+	+	+	+	+	+	+	0	+	Crippled	4 7/12	11 7/12	
14	7 0/12	M	+	+	+	+	+	+	+	+	0	+	+	+	Active	1 6/12	8 8/12	
15	7 1/12	F	+	0	+	+	0	+	0	0	0	0	0	0	Well	1 7/12	8 8/12	
16	7 2/12	F	+	+	+	+	+	+	+	+	+	0	0	0	Dead	3 3/12	10 5/12	Unknown
17	7 7/12	F	+	+	+	+	+	+	+	+	+	+	+	0	Dead	1 3/12	9 0/12	Perforated G.I. ulcers
18	7 8/12	M	+	+	+	+	+	+	+	+	+	+	+	+	Dead	8 10/12	16 6/12	Respiratory
19	7 10/12	M	+	0	+	+	+	+	+	+	0	0	0	+	Well	18 8/12	26 6/12	
20	8 1/12	M	+	+	+	+	0	+	+	+	0	+	+	0	Active	1 0/12	9 1/12	
21	8 8/12	F	+	+	+	+	+	+	+	+	0	0	0	0	Well	3 8/12	12 0/12	
22	9 7/12	M	+	+	+	+	+	+	+	0	+	0	0	0	Active	1 0/12	10 7/12	
23	9 11/12	F	+	+	+	+	+	+	0	0	0	0	±	0	Well	1 1/12	11 0/12	
24	10 9/12	M	+	+	0	+	+	+	+	0	+	0	0	0	Dead	9/12	10 9/12	Respiratory
25	10 9/12	F	+	+	+	+	+	+	+	+	+	+	+	0	Dead	4/12	10 7/12	Probably respiratory
26	10 7/12	M	+	+	+	?	+	+	+	+	?	+	?	?	Dead	2 2/12	12 9/12	Unknown

onset was acute. This was usually associated with extensive involvement, a rapidly progressive course, and a fatal outcome. No consistent precipitating factor could be elicited by history in any of the children, although in two cases (Cases 1 and 14) exacerbations occurred concurrently with manifestations of drug sensitivity to sulfadiazine and penicillin.

The commonest early symptoms (Fig. 1) were weakness and easy fatiguability. In only two of the 26 children was weakness not noted at some time during the course of the illness. This weakness was frequently associated with muscle stiffness, usually noted

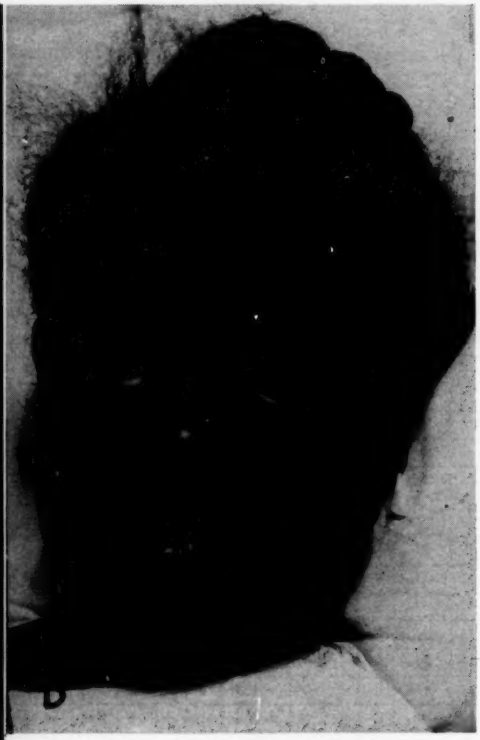

FIG. 1. Case 2 (A), showing marked weakness, moderate contractures and generalized edema in acute phase of disease.

FIG. 2. Case 25 (B), showing facial edema. Butterfly area of induration was present in this patient.

initially in the lower extremities, and soreness and pain in the muscles and occasionally in the joints. The gait was often described as "awkward," "shuffling" or "unsteady." The weakness was sometimes slight but often was so extensive that the patient could not sit up, hold up his head or even roll over in bed. All the muscles of the trunk, extremities and face have been involved to varying degrees. Usually, though not invariably, the process was irreversible when weakness was extensive and then it either terminated fatally or ended in marked crippling. However, moderately severe weakness was compatible with recovery of good function (Case 19). Deep tendon reflexes occasionally were absent when muscle weakness was extreme.

The most critical factor in respect to survival was the degree of involvement of the

muscles of respiration and deglutition. Weakness of these muscles was noted in 13 of the children and was the cause of, or contributed to, the fatal outcome in at least 5. Diplopia occurred in one patient (Case 24).

Fever ranging from "low grade" to 39.5° C. was noticed early in the disease in 11 children. However, even excluding periods of superimposed infection, 21 of the children were febrile during the course of the disease at one time or another.

Involvement of the skin of the face was observed in 23 of the 26 children and was usually present early in the disease. The characteristic lesion was a violaceous or erythematous discoloration of the upper eyelids (occasionally periorbital in distribution) associated with periorbital edema which at times extended to involve the nasal bridge, the malar areas and the upper lip (Fig. 2). These changes were occasionally so faint as almost to escape notice or so flagrant as to suggest the diagnosis of disseminated lupus erythematosus (table 2). At times the erythematous lesions also involved the skin over the anterior chest and there was fine scaling of the involved areas. In the milder form

TABLE 2

INITIAL DIAGNOSIS MADE IN 26 CHILDREN WITH DERMATOMYOSITIS

Initial Diagnosis	No. of Children
Dermatomyositis	8
Disseminated lupus erythematosus	4
Muscular dystrophy	3
Rheumatic fever	2
Poliomyelitis	2
Diffused myelitis	1
Peripheral neuritis	1
Trichinosis	1
Schleroderma	1
Adrenal hyperplasia	1
"Neurologic disorder"	1
Periarteritis nodosa	1

the lesions consisted merely of induration over the malar prominences and/or periorbital edema. Photosensitivity of the facial lesions was noted in only five children.

Changes in the cutaneous and deep tissues were also prominent in the extremities. The skin appeared tight and glossy or scaly. On palpation, tenderness was often demonstrable, and the skin, subcutaneous tissue and muscle felt thickened, leathery, indurated, brawny or inelastic in varying degrees. In a few of the children generalized edema, which pitted poorly, was present, and in these patients particularly decubitus ulcers tended to occur in spite of careful nursing. Later in the disease extensive atrophy was observed; at this stage the skin appeared tightly bound to the underlying tissue, and the fingers showed tapering (a Raynaud-like atrophy) and contractures. Also characteristic of the disease were lesions which occurred over the extensor surfaces of the joints, particularly the knuckles, elbows and knees. These areas appeared erythematous, atrophic and scaly with a network of fine blood vessels visible; occasionally vesiculation was present. Later these areas often became either pigmented or depigmented (Fig. 3). Lesions of the mucous membranes including edema, hemorrhage, vesiculation and ulcerations have been reported by Kiel[12] and were noted in 2 children in this series.

Deposits of calcium, apparently secondary to necrosis, were found late in the disease in the muscle, fascia and subcutaneous tissue in 7 of the children (Cases 3, 5, 10, 13, 14, 18, 19; see Fig. 4); these developed in all but 2 children followed for over 4 years. When extensive this secondary condition has been included in the syndrome of calcinosis universalis. In one of the children (Case 18) stony hard plaques were present throughout the entire abdominal wall and much of the rest of the body. In others only small pea-sized nodules of calcium were found (Fig. 5). In most of the children with calcium deposits the overlying skin broke down, and the nodules were extruded in either solid or semisolid form.

In those patients who survived the disease, the major factor contributing to disability was the degree of contracture of the extremities. Initially mild to moderate limitation of motion of the joints was seen in most cases. This progressed to severe deforming and crippling contractures (Fig. 6) in 8 of the children and to milder degrees of disability in others (Fig. 7).

While adenopathy was noted in several cases, it was not found more frequently than in the general pediatric population. Hepatomegaly was found in only 3 cases and splenomegaly in only 2. Cardiac abnormalities have been described.[13, 14] In one case questionable cardiac enlargement and a blowing systolic murmur were noted terminally (Case 25). Electrocardiograms taken in this patient 1 and 2 months before death were within normal limits, and an autopsy was not performed. In another child (Case 14) the ECGs suggested myocardial involvement (prolonged electric systole, depressed ST segments in leads 1, 2 and 3 and inverted T-waves in chest leads), but there was no other evidence of cardiac disease.

Like the course of adult dermatomyositis, the disease in the present series of children was only occasionally characterized by a series of remissions and relapses; in most of the cases exacerbations did not occur once the process became quiescent. In fact, from

FIG. 3. Case 8, showing chronic skin changes over knuckles, with pigmentation, depigmentation and scaling. Moderate degree of atrophy of hands is evident.

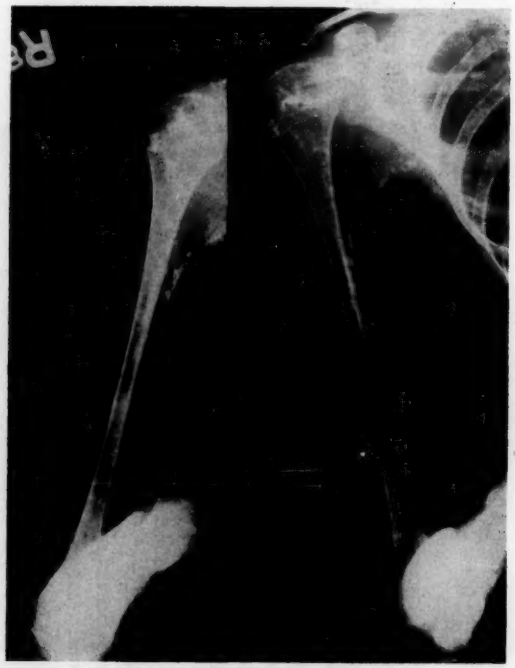

FIG. 4. RG from Case 18 showing extensive calcification of soft tissues and marked osteoporosis.

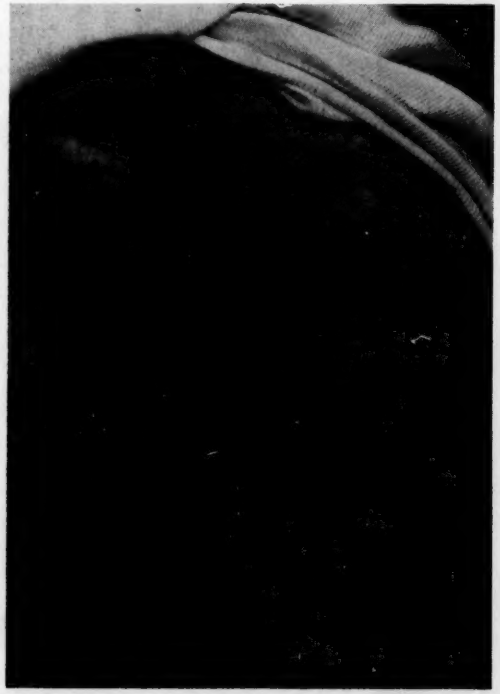

FIG. 5. Pea-sized calcific nodule being extruded through skin of buttock of Case 19.

FIG. 6. Case 18 showing late stages of generalized dermatomyositis, with extreme wasting, extensive muscular atrophy, crippling contractures and edema of lower extremities. Subcutaneous calcified nodules can be seen over elbows and abdomen.

the series of adults with dermatomyositis reported by O'Leary and Waisman[13] and by Sheard[15] it is apparent that the disease in adults and children is very similar with comparable signs and symptoms, course, morbidity and mortality, and pathologic findings.

LABORATORY FINDINGS

In reviewing the mass of laboratory data accumulated, it became apparent that no laboratory procedure except a biopsy was useful. The clinical picture is uniform enough to suggest and usually to establish the diagnosis, and the biopsy is confirmatory. Examination of the blood showed no variation from the normal except for occasional mild anemia and an eosinophilia in 5 patients in whom trichinella skin and serologic tests were negative. The white blood count was only significantly elevated when superimposed infection was present. The sedimentation rate was elevated in 12 of the 19 cases in which the determination was made. A variety of blood chemical measurements* in 14 patients, including those with calcinosis universalis, were invariably within normal limits. Liver function studies performed in 4 patients were normal. The antistreptolysin titre of the serum from 7 patients during the acute phase was not elevated. In contrast to almost all proved cases of disseminated lupus erythematosus in children, the urinary findings were consistently within normal limits except for one child (Case 14) with transient hematuria concomitant with a high urinary calcium concentration. Eighteen patients had examinations of the cerebrospinal fluid, all with normal findings. Electrocardiograms were done in 16 children without any abnormalities, except in the one child (Case 14) previously mentioned. Initial RGs were either normal or showed moderate osteoporosis, the latter finding undoubtedly being related to immobilization. Later in the disease calcinosis could be demonstrated roentgenographically (Fig. 3) and was extensive in some cases.

The urinary excretion of creatine and creatinine was measured in 11 patients, and in almost every case there was an increase of creatine excretion. According to Peters and Van Slyke[16] "spontaneous creatinuria accompanies all conditions attended by atrophy or extreme functional disorders of the skeletal musculature." Hence the creatinuria found in these cases of dermatomyositis did not have any specific diagnostic or prognostic value.

DIFFERENTIAL DIAGNOSIS

Disseminated lupus erythematosus (table 2) was the disease most commonly confused with dermatomyositis in the present series. Two of the cases in this series were

* These included NPN, Na, K, Cl, CO_2, Ca, P, alkaline phosphatase, pH, T.P., and A/G ratio.

actually followed for a period of years before the correct diagnosis was established. The authors feel that the two diseases in their typical forms have little in common except for the occurrence of facial rashes, and even these are usually dissimilar when examined closely. The rash in dermatomyositis is often periorbital, more violaceous than erythematous, more indurated and less pronounced than the butterfly rash of disseminated lupus erythematosus. In addition muscular weakness in dermatomyositis is almost invariably a primary part of the disease, whereas any weakness found in disseminated lupus erythematosus is secondary to the systemic manifestations of the disease and is usually less striking. The brawny induration of the subcutaneous tissue and muscle in dermatomyositis is not seen in lupus erythematosus, and pain in disseminated lupus erythematosus is usually secondary to joint involvement, while that found in dermatomyositis is due to involvement of the muscles. Leukopenia and renal involvement found frequently in disseminated lupus erythematosus are absent in dermatomyositis. A muscle biopsy, while

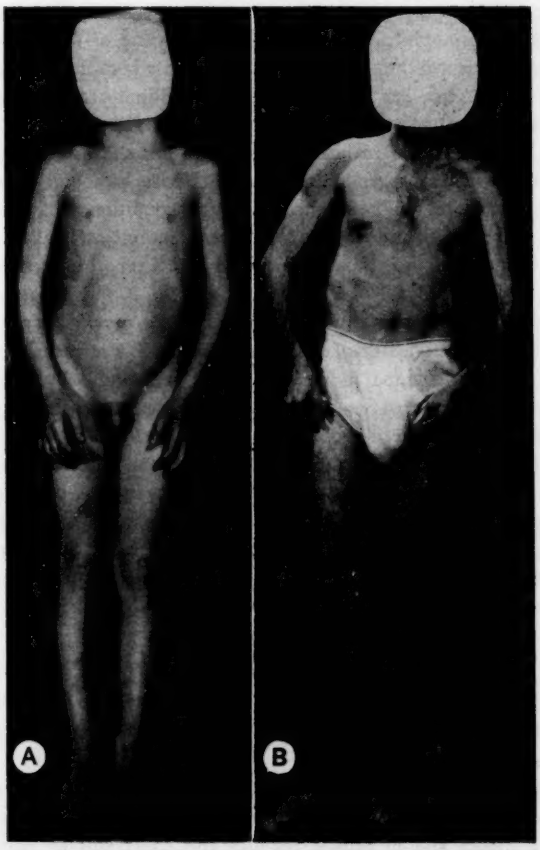

FIG. 7. Case 19, at ages of 9 and 27 yr. At 9, skin lesions over knees and hands and contractures can be seen. At 27, full growth and development is evident, although forearms and hands show some sequelae of disease. Over left costal margin calcified plaque is visible.

not specific, may be useful in further distinguishing these two diseases, and the recently described test for the "L. E." cell[17] has regularly been negative in dermatomyositis in the authors' experience. A review of all cases of disseminated lupus erythematosus seen at the Children's Medical Center has revealed no instance of both diseases coexisting in the same patient.

Early in the disease the differential diagnosis between dermatomyositis and diffuse scleroderma may be difficult, and even a biopsy may not provide a definitive answer. However the predominance of muscular weakness, pain and tenderness in the acute early phase of dermatomyositis is in contrast to the usual predominance of skin involvement in scleroderma.[18]

Poliomyelitis, myasthenia gravis, muscular dystrophy and other neuromuscular diseases have been confused with dermatomyositis, but usually a brief period of observation and study will differentiate these conditions. In the initial stages of dermatomyositis, trichinosis may be considered, but usually the history, the appearance of subconjunctival hemorrhages, the acute onset and a positive trichinella skin test will identify the latter, in spite of the occurrence of eosinophilia in 10 to 20% of the cases of dermatomyositis.

The authors have reviewed the cases of five children in whom the diagnosis of localized dermatomyositis or morphea has been made. These children presented discrete areas of induration of the skin and subcutaneous tissues, muscular atrophy and local contractures, without any of the generalized manifestations; none has shown the skin rash seen so frequently in children with the generalized disease. Hence, although pathologic similarities may be found on biopsy of the affected parts, this condition does not appear similar to the disease described in this series, and would seem more closely allied to scleroderma and other related conditions. It is thus not included in this report on generalized dermatomyositis.

It is to be noted that none of the patients in this or any previous series was an infant. The possibility that dermatomyositis may occur in infancy was raised by three patients whose physical findings included induration of the skin and subcutaneous tissue and muscular weakness. The onset of symptoms in these three infants was at or shortly after birth. Biopsies showed widespread subcutaneous edema and focal degeneration of muscle fibers. During their course in the hospital no skin rashes were observed, and the induration did not change. However the muscular weakness became profound and all died in respiratory failure. Postmortem examination was performed on only one of these infants, the main finding being muscle degeneration. Subsequently a sibling of this patient died with classical Werdnig-Hoffman disease and a review of the postmortem findings demonstrated a marked similarity of the muscle lesions. It is therefore felt that these infants probably do not represent the syndrome under discussion.

Pathology

The material for study consisted of biopsies from 23 patients and two postmortem examinations.

The type of skin and muscle lesion seen microscopically was closely correlated with the duration of the disease. The earliest lesion showed extensive edema of the subepithelial connective tissues and of muscle bundles and collections of polymorphonuclear leucocytes in both skin and muscle. These were mainly eosinophilic but in a few neutrophils predominated. In none of the sections was there simple edema without cellular

response. Most often the early lesion was a diffuse process although foci of necrotic muscle fibers with concomitant inflammatory cell collections were seen at all stages of the disease.

After this early reaction a progression of pathologic changes was noted. In sections of skin and fascia, foci of lymphocytes and monocytes were demonstrable, mainly subepithelially and at the interfaces between fascial bands and muscle, and between fat lobules and their fibrous envelopes. A few foci were perivascular. No fat necrosis was seen. Necrosis of the muscle, on the other hand, was a frequent finding in association with similar focal collections of lymphocytes and monocytes. Some muscle fibers disappeared apparently by resorption, resulting in a relative increase in the number of sarcolemmal nuclei. No sign of regeneration of muscle was seen. Later changes in skin and subcutaneous tissue consisted of a marked increase in the fibrous elements, so that areas of thick matted scarring occurred. Over these areas the skin was atrophic and hair follicles and sebaceous glands were diminished in number. Intense scarring occurred in the fascia also, and occasionally calcifications occurred in plaques in relation to subcutaneous or fascial scar. In these areas the fibrous tissue seemed necrotic or hyalinized, but no inflammatory reaction attended the calcification. Late in the disease, continuing atrophy and disappearance of muscle fibres without inflammation or calcification was the usual histologic picture.

Vascular lesions vary in degree in different patients and in different areas of the same patient (whether they are always present in all patients cannot be stated with certainty because much of this analysis is based on biopsy material). Typically, the involved vessels are muscular arterioles, although small muscular arteries may also be affected. Smaller vessels show internal or medial proliferation, occasionally with hyalinization. Granular internal deposits suggesting platelet clusters are often seen, and occasionally thrombosis occurs. The lesions may thus be difficult to distinguish from those of scleroderma or thrombotic thrombocytopenic purpura, but ordinarily differ from those of anaphylactoid purpura or polyarteritis nodosa in that necrosis and inflammation of the vessel walls proper is slight or absent. Occasionally, much of the muscle damage found appears to be anoxic or infarct-like, rather than simply inflammatory, and cutaneous or esophageal ulcers occasionally appear to be the result of the arteriolar lesions.*

Biopsies from children with localized dermatomyositis or morphea in contrast show fibrosis of fascia, intermuscular septa, and subepithelial connective tissue, and atrophy of the skin, but no inflammatory foci or areas of calcification. However, the pathologic end result of the localized and generalized forms of dermatomyositis may be similar with regard to a single region.

Therapy

A great variety of therapeutic measures have been used in generalized dermatomyositis, mostly without effect (table 3). The only definitely effective measure at the present time appears to be orthopedic treatment combined with vigorous physiotherapy. The object of such therapy has been to prevent the formation of contractures and deformities or to correct them once they have occurred. Traction, casts, splints and corrective opera-

* Three dermatomyositis patients have been seen with premortem gastrointestinal hemorrhage and postmortem esophageal or intestinal ulceration, presumably secondary to the vascular lesions.

tive procedures have all been used with success. Obviously it is of the utmost importance to treat the children from a prophylactic point of view and to make every effort to avoid contractures. Therefore, in the early stages of the disease, two elements of treatment are emphasized: (1) correct positioning to prevent deformity and (2) a balanced program of rest and motion so that the inflamed muscles and fascia heal and yet retain mobility. Even with this form of therapy patients with extensive muscular involvement may become bed-ridden. However, in some cases insufficient treatment, initiated at times too late has possibly contributed to later disability. Although those patients with palatal and respiratory involvement present a further problem not amenable to orthopedic measures, even in these patients prevention of deformities should be stressed since recovery may occur.

TABLE 3

TABULATION AND EVALUATION OF VARIOUS FORMS OF THERAPY USED IN 26 CHILDREN WITH DERMATOMYOSITIS

Therapy or Treatment	Evaluation				
	Helpful	Possibly Helpful	Insufficient or of No Benefit	No Benefit	Total
Physiotherapy or orthopedic measures	6	6	12		24
Respirator	1				1
Testosterone		10		2	12
Adrenocorticotropic hormone		5		2	7
Cortisone		4			4
Ergostanyl acetate				4	4
Vitamin E				3	3
Pituitrin				1	1
Thyroid				1	1
Insulin				1	1
Potassium iodide				1	1
Cane juice				1	1
Para-amino-benzoic acid				1	1

Final evaluation of a number of therapeutic agents is difficult because of the small number of cases in which each has been used. Vitamin E (Cases 1, 7, 13), ergostanyl acetate (Cases 11, 13, 18), para-aminobenzoic acid (Case 7), cane juice (Case 13), insulin (Case 19), pituitrin (Case 5), potassium iodide (Case 5), thyroid (Case 5) have all been tried without significant benefit to the patient.

Various workers have experimentally produced lesions in animals which have been considered analogous to the pathologic findings in dermatomyositis. Thus the demonstration of a nutritional muscular dystrophy in vitamin E-deficient rabbits[19] and the muscle stiffness syndrome in guinea pigs deprived of a fat-soluble factor in the diet, which has been prevented by giving ergostanyl acetate or cane juice[20, 21] has suggested the use of these compounds in this disease. None of these factors, however, has proved of value in the patients in this series.

The postulate that there exists a relationship between the light sensitivity found in disseminated lupus erythematosus, dermatomyositis and in some patients receiving

sulfonamides[22] led to the suggested therapeutic use of para-aminobenzoic acid, a metabolic antagonist to the sulfonamides. This drug is toxic, and evidence for its efficacy in this disease is limited and unconvincing. The one child (Case 7) of this series treated with para-aminobenzoic acid showed no improvement and in fact died of acute toxic hepatitis.

The use of endocrine therapy in this disease has been described.[23-29] Two of the children who were previously reported to have shown a response to adrenocorticotropic hormone[28] have been included in the present series (Cases 8, 20), and it is felt that on further follow-up the response can be classified as suggestive only. Of the remaining 11 patients cited in the literature treated with adrenocorticotropic hormone, four apparently had a dramatic response with remissions lasting up to four months. Three of these patients had an acute and fulminating form of the disease. The other seven children showed only equivocal improvement.

The evaluation of hormonal therapy in the children in this series is difficult because of the variety of regimes, doses and hormones employed and because of the occurrence of spontaneous remissions in the natural course of the disease. Seven of the children (Cases 2, 8, 13, 15, 21, 22, 23) were given adrenocorticotropic hormone.* In addition two of these same children (Cases 15, 22) were given a prolonged course of testosterone† which was started before the adrenocorticotropic hormone was discontinued, and it is impossible to differentiate between the effects of the two agents. In four children (Cases 1, 8, 14, 17) cortisone‡ was used. In one of these children (Case 14) testosterone was used concomitantly. In eight children (Cases 1, 2, 6, 8, 9, 18, 21, 23) testosterone was given separately. The adrenocorticotropic hormone was used in dosage of approximately 100 mg./day i. m. for 2 to 3 weeks; the cortisone in dosage of 50 to 200 mg./day depending upon the size of the child and the route of administration; the testosterone in doses of 30 to 50 mg./day for periods of one to 12 months. In some cases this dose of testosterone was sufficient to produce virilization. In most of the children adrenocorticotropic hormone or cortisone was given in the acute stage and was followed by the administration of testosterone in the hope that any improvement induced by the first two agents might be sustained by the latter.[28, 30]

Treatment with adrenocorticotropic hormone, cortisone and testosterone alone, or in combination, appears to have no effect on the disease of those patients who have crippling residua and a relatively inactive process. However, in at least three of the children (Cases 1, 9, 17) with an acute and active disease there was striking and rapid symptomatic improvement following the administration of these hormones. The improvement seen in these children was characterized by a decrease in fever, subsidence of skin lesions, diminution of muscle pain and tenderness and an increase in muscle strength, appetite and weight. In seven children (Cases 6, 8, 14, 15, 21, 22, 23) with active but less acute disease gradual improvement occurred concomitantly with the administration of these

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* Adrenocorticotropic hormone used in some of these cases was supplied through the courtesy of Dr. John R. Mote of Armour and Company, Chicago.

† Testosterone propionate linguets were supplied by the Ciba Manufacturing Company, Summit, N.J.

‡ Part of the cortisone used in these patients was supplied through the courtesy of Merck and Company, Rahway, N.J.

agents. It is noteworthy that many of these children had had their disease for weeks prior to therapy without improvement, and in some, before therapy, the course of the disease had been steadily downhill.

While none of these children treated with steroids has been followed long enough for final evaluation, and evidence of the therapeutic effect in no individual case can be considered conclusive, the moderately consistent, at least temporary, benefit following administration of these hormones suggests some response to the therapy. Symptomatic improvement was undoubtedly induced by adrenocorticotropic hormone and cortisone administration. The fact that two children (Cases 8, 17) who had an initial favorable response to endocrine therapy later succumbed to the disease demonstrates that these agents do not necessarily change the course of the disease and that the temporary benefits may be merely symptomatic. However, the high morbidity and mortality of untreated dermatomyositis would seem to justify the therapeutic trial of these hormones, particularly in the acute forms of the disease, in spite of possible dangers. Even if the response is only symptomatic, relief of pain will make the patient more amenable to physiotherapy and orthopedic procedures, thus helping to prevent the crippling residua that occur.

From this experience with steroid therapy in children with dermatomyositis the following regime is suggested. Initial treatment of the child with active disease should consist either of adrenocorticotropic hormone in doses of 100 mg./M^2/day* in divided intramuscular doses, or cortisone 100 mg./M^2/day intramuscularly or orally. During this period the child should be placed on a low sodium diet and given supplemental potassium. The weight should be followed carefully for the appearance of edema, the blood pressure taken daily and serum electrolytes followed. These precautions are necessary since undesirable effects may occur, such as the development of electrolyte and fluid disturbances with sodium retention and potassium deficiency, hypertension, activation of latent diabetic tendencies, psychologic disturbances, especially hypomania, and the changes of Cushing's syndrome. In addition, it should be noted that the analgesic and antipyretic effect of the steroids may mask signs of infection and intestinal perforations.[31] (The intestinal ulcerations seen on postmortem examination in Case 17 may have been related to steroid therapy.)

This therapeutic regime should be continued for 10 days to 3 weeks, depending upon the response of the patient. At the end of this period the dosage should be very gradually diminished, and testosterone propionate in doses of 40 mg./M^2/day given by sublingual tablets or the equivalent in other testosterone preparations should be initiated. By this technic the rebound effects of sudden withdrawal of therapy and resultant exacerbations may be avoided. The testosterone therapy should be continued for several months, or until the disease appears quiescent. During this period evidence of virilization may be expected. As in one patient in the present series, the prolonged use of methyl testosterone may lead to intrahepatic obstructive hepatitis.[32]

It has been interesting to note that in one of the children (Case 3) the onset of a remission was chronologically related to an operative procedure. It is intriguing to speculate that an alarm reaction with increased endogenous production of adrenal hormones may possibly have influenced the course of the disease.

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* M^2 refers to square meters of body surface area.

In those cases with respiratory and palatal involvement, treatment aimed at maintaining adequate air exchange may be life-saving. Suction and postural drainage are important, and a respirator should be available. One of the children (Case 8) required a respirator for more than two months, although later she was able to survive 18 months without this aid. Gavage feeding may be necessary to maintain nutrition and meticulous skin care is essential to prevent decubitus and intertrigenous ulcers.

There is at present no known effective therapy for the secondary complication of calcinosis universalis. Partial parathyroidectomy (Case 19) was performed once without benefit and a low phosphorus diet in one child (Case 10) was without effect. The mechanism which leads to calcium deposition is necrosis of the subcutaneous, fascial and muscle tissues.

Summary and Conclusions

Twenty-six cases of dermatomyositis in children with follow-up studies ranging from one to 19 years are presented in order to indicate the natural history of this disease.

Of these 26 children, 10 are dead, 4 still have active disease, 4 have crippling contractures and 8 are able to lead an active normal life.

Thirteen of the children received endocrine therapy with adrenocorticotropic hormone, cortisone or testosterone. This appeared to produce at least symptomatic benefit in some cases, particularly early in the course of the active disease and, coordinated with symptomatic care, helped to tide the patients through the acute stages.

The most important treatment consists of persistent orthopedic measures and physiotherapy to minimize contractures.

Since death in this disease often results from palato-respiratory involvement, maintenance of an adequate airway and the use of a mechanical respirator may be life-saving.

Case Reports

Examples Illustrating Representative Forms of the Disease

Dermatomyositis With Remissions and Relapses:

Case 1 was a white boy who first had weakness, pain and edema in his legs and feverishness at the age of 2-3/12 yr. He was initially diagnosed as having poliomyelitis, was treated with braces and finally after 6 to 8 mo. appeared entirely well. At 3-5/12 yr. he had a recurrence of generalized muscle pain and weakness without fever. At that time brawny induration was noted in the muscles of the extremities, the typical facial rash was present and he became so weak that he could only sit up by pulling on the sides of the bed with his hands. By history this exacerbation was possibly associated with a sulfadiazine reaction. Laboratory data including lumbar puncture and pneumoencephalogram were within normal limits except for an elevated sedimentation rate which persisted during all his exacerbations. A biopsy was consistent with dermatomyositis. Within 6 mo. with only physiotherapy he had made a remarkable improvement being able to run and play and only showing slight residua. Minimal exacerbations occurred 2 to 3 times a year until the age of 5-1/12 yr. when a flare-up concomitant with an attack of tonsilitis necessitated hospitalization and was followed by chronic low-grade fever and contractures of his hip and knee joints. Again a remission ensued spontaneously after 4 to 5 mo. and lasted for 2 yr. He then, 5 yr. after the onset of the disease, had another exacerbation. Treatment with oral cortisone coincided with improvement in strength and, when the hormone was withdrawn, the disease again progressed. A second course of cortisone followed by testosterone again coincided with improvement which persisted for 5 mo. During that period temporary withdrawal of testosterone was apparently associated with a moderate increase in the signs of the disease. Another exacerbation, the fourth major exacerbation, was further complicated

by methyl testosterone-induced obstructive jaundice. Hormonal therapy was then discontinued and over the course of 3 mo. there was a gradual spontaneous improvement. At the age of 8-2/12 yr., almost 6 yr. after the onset of the disease, the child was in remission but had been left with considerable muscle atrophy and consequent weakness, and some moderate limitations of joint motion. However, in spite of this he was active and riding a bicycle. He was considered still to have potentially active disease in spite of the fact that some of his acute episodes have apparently, at least symptomatically, responded to hormonal therapy.

Dermatomyositis with Respiratory and Palatal Involvement:

Case 2, a white boy, was first seen at the age of 3-7/12 yr. Because of progressive weakness and muscular pains, the diagnosis of poliomyelitis had been made initially 5 mo. earlier. Physical examination showed a child with generalized edema, atrophic changes over the knuckles and knees, a typical facial rash with periorbital edema, brawny tissues, intertriginous and decubitus ulcers, and marked generalized weakness (Fig. 2). There was definite mild contracture of the elbows, hips and knees and limitation of motion of the fingers. Hemogram, urinalysis, and examination of the cerebrospinal fluid were all normal. Sedimentation rate (Westergren) was 44 mm./hr. Roentgenograms of the bones showed marked osteoporosis and the ECG was normal. A biopsy taken confirmed the clinical diagnosis of dermatomyositis.

The patient was treated with testosterone propionate and physiotherapy, without benefit. He ran a downhill course, with progression of the weakness, edema, and contractures. Seven months after the onset of the disease he could barely speak and required frequent suction to keep his airway clear and terminally he required gavage feedings.

During this terminal period he was given a 20 day course of adrenocorticotropic hormone. There was a definite diuresis, with 1.8 kg. weight loss while on this therapy, but otherwise only the very slightest improvement in his general condition. The patient died 9 mo. after the onset of his disease, and an autopsy confirmed the diagnosis of generalized dermatomyositis and aspiration pneumonia.

Dermatomyositis with Endocrine Therapy and Eventual Death:

Case 17, a white girl, developed redness and swelling of the upper eyelid at the age of 7-7/12 yr. Following this there was noted the onset of weakness, severe pains, "stiffness" of the legs, and a tendency to be easily fatigued. Two months after the onset of symptoms an erythematous rash appeared over the knees, forearms and hands, and pain was also noted in the upper arms and shoulders. Within a few weeks a low grade fever appeared, the child became anorexic, and had difficulty with deglutition. For these reasons she was admitted to the Children's Medical Center.

On admission the child had a low grade fever (38.4°C.) and appeared chronically ill. There was definite weakness of the arms and legs. Over the face, in the butterfly distribution, was a scattered erythematous rash. The eyelids were discolored and the periorbital tissues were swollen. There was also an erythematous eruption involving the bony prominences of the knuckles, elbows, knees and ankles. Movement of the extremities was limited by pain. The muscles were tender and had a brawny indurated feeling on palpation.

Hemogram and urinalysis were normal. The sedimentation rate (corrected Wintrobe) was 29 mm./hr. Blood chemistries, including NPN, pH, CO_2, sodium, chloride, calcium, phosphorous, potassium, phosphatase, total protein and A/G ratio were within normal limits. Febrile agglutinins were not present and tuberculin and trichinella skin tests were negative. Liver function tests were normal. An incubated bone marrow specimen showed no "L.E. cells." Antistreptolysin titre was less than 50 units. A biopsy of the skin and muscle was consistent with dermatomyositis.

During a 25 day course of cortisone at dosage starting at 200 mg./day by mouth, and tapered to a maintenance dose of between 50 and 100 mg./day, a striking but probably nonspecific improvement was noted. The low grade fever dropped to normal range, the skin lesions faded, the pain decreased, appetite increased and there was a weight gain from 23 to 26 kg. It was felt that there might have been some increase in muscle strength, but this could have been related to the decrease in pain on moving the muscles.

When the cortisone was discontinued there was a prompt return to the status seen on admission.

She was then started on testosterone linguets at a dose of 40 mg./day which was not taken well because of some behavior difficulties. However when the testosterone was administered parenterally, 10 mg. aqueous suspension daily i.m., again a striking improvement was noted, similar to that seen with cortisone. Eighteen days of testosterone at this dosage produced definite signs of virilization. The dosage was decreased to 5 mg./day. On this regime the patient remained afebrile, with minimal pain and tenderness, and the skin lesions continued quiescent. Active physiotherapy and orthopedic care was carried out. Suggestive evidence of possible activity of the disease was the presence of some periorbital and pretibial edema, and some slight residual skin lesions.

After 20 days on testosterone the patient was transferred to a convalescent home. At this home the patient was taken off testosterone and placed again on cortisone, 100 mg. every 1 to 3 days. She apparently did well on this regime, for 6 mo. later, when the patient was 8-8/12 yr. old, the mother wrote that she was gaining strength, could stand, that her arms and legs were "loosening up" and that her appetite and weight gain were "good." Two months later the cortisone was discontinued. Two weeks after discontinuation of the hormone the child suddenly developed abdominal pain, fever and frequent loose and tarry stools. She was placed on adrenocorticotropic hormone and shortly thereafter transferred to the Grace-New Haven Community Hospital. On admission to that hospital the patient again showed the facial rash, skin lesions over the rest of the body and marked contractures. She ran a low grade fever. The hemogram was not unusual, but urinalyses were routinely loaded with white cells and albumin.

The child went downhill rapidly. A further episode of acute abdominal pain, associated with grossly bloody stools and urine occurred. In spite of antibiotics and intravenous fluids and transfusions she died at the age of 9 yr., 17 mo. after the onset of her disease. Postmortem examination showed changes consistent with dermatomyositis, slight hirsutism and enlargement of the clitoris, multiple perforated esophageal, gastric and duodenal ulcers, hemorrhages into the kidneys and ureters and pneumonia.

Dermatomyositis with Severe Crippling and Calcinosis:

Case 18, a white boy, was first seen at the Children's Hospital at the age of 2 yr. because of nonthrombocytopenic purpura and arthritis (Schoenlein's purpura) which lasted 1 wk. Thereafter he was well until the age of 7-8/12 yr. when irritability, weakness, unsteady gait and a tendency to fatigue easily developed insidiously. In addition the boy had an erythematous blush over the malar prominences, periorbital edema, and scaling erythematous lesions over the knuckles, elbows and knees. The rash later involved the chest, muscle pains developed and weakness progressed associated with more and more muscular atrophy. When admitted to the Children's Hospital 1 yr. after the onset, the patient showed striking weakness, being unable to walk and just able to pull himself out of bed. He was hospitalized for 2 wk. during which time the erythematous lesions were shown to be photosensitive; he had a low-grade fever, and a presumptive diagnosis of disseminated lupus erythematosus was made. Hemogram and urinalysis were normal as was the cerebrospinal fluid. The sedimentation rate (Westergren) was 33 mm./hr. and the antistreptolysin titer was 100 units (upper limits of normal 250 units).

However, over the course of the next 2 yr., generalized contractures developed, peripheral edema appeared, fever continued, brawny indurated tissues were noted, and the patient became completely bed-ridden. He was hospitalized many times at various hospitals. Finally, a biopsy was done during one of these admissions and established the diagnosis of dermatomyositis. At the age of 10-6/12 yr. he showed the classic picture of late crippling generalized dermatomyositis (Fig. 6) with wasting, contractures, indurated skin, edema, and calcification of subcutaneous tissues and muscles.

Fasciotomies, tendon lengthenings, traction, casts were all used in an effort to correct the deforming contractures. Ergostanyl acetate and testosterone were used without benefit and the boy's condition progressed until 8-10/12 yr. after the onset of the disease he was desperately crippled and deformed, had great difficulty with respiration and deglutition. He lay in bed, his thoracic cage collapsed, his back fixed in hyperextension, and he was completely immobilized by contractures and tissue calcification. Often these calcific plaques were extruded through the skin and decubitus ulcers appeared in spite of constant nursing attention. During this late stage of the disease a course of testosterone therapy was given, without any apparent effect, for finally in one of many recurrent episodes of respiratory difficulty and aspiration he died, at the age of 16-6/12 yr.

Dermatomyositis with Extensive Disease and Functional Recovery:

Case 19 was a white boy in whom a brilliant violaceous flush over the face, periorbital edema and slowness in walking were noted at the age of 7-10/12 yr. Gradually weakness increased, hip pains developed and an erythematous scaly rash over the knuckles and knees appeared. One year later physical examination showed, in addition, low-grade fever, great weakness, muscular atrophy, and contractures of the elbows and hips. When he tried to get up, he had to roll to the prone position and support himself in standing with his hands on his knees. Hemogram, urinalysis, examination of the cerebrospinal fluid and an ECG were all within normal limits. Roentgenograms at that time revealed no evidence of abnormal calcium deposits. A biopsy substantiated the diagnosis of dermatomyositis. He was given physiotherapy, a diet containing rare meat, and intravenous insulin with very little improvement. His disease was characterized by apparently spontaneous remissions and exacerbations, without progression of muscular involvement. Between exacerbations he was usually able to walk.

At the age of 11 yr., approximately 3-6/12 yr. after the onset of the disease, subcutaneous plaques and nodules appeared. These seemed most obvious in the finger tips, but were present over the entire body. Intermittently what appeared to be calcium salts were extruded from these areas in solid or semisolid forms. In spite of the apparent termination of the active phase of the disease at the age of 14 yr., the patient continued to be disabled by these calcium deposits. A secondary diagnosis of calcinosis universalis was made at the age of 15 yr., and a partial parathyroidectomy was performed at another hospital. When the patient was 16 yr. old the number of calcium deposits began to decrease, and encouraged by this, he began to take strenuous physiotherapy.

At the present time at the age of 26-6/12 yr., almost 19 yr. after the onset of the disease, the patient is engaged in active work as a clerk, goes to night school and is functionally well. His residua consists of atrophy of some of the muscles in the forearms and hands, some minor contractures and thickening of the tissues of the face and ears (Fig. 7) and in addition small but diffuse calcified plaques and nodules (Fig. 5) which are easily demonstrated on roentgenogram but cause no discomfort. His muscular strength is excellent.

Dermatomyositis with Complete Remission Coincident with Endocrine Therapy:

Case 21 was a white girl who developed areas of erythematous and roughened skin over the knuckles, elbows and knees at the age of 8-6/12 yr. and shortly thereafter a typical butterfly rash and periorbital edema accompanied by a low-grade fever. She became irritable, was easily fatigued and complained of a stiff and painful back and weak legs. When seen at the Children's Hospital 5 mo. later she showed in addition to the classical skin and tissue changes, nodules over the flexor surfaces of the forearms, moderate contractures of the elbows, hips, knees, and ankles, and such weakness that she could not step up onto a chair without aid. A biopsy confirmed the clinical impression of dermatomyositis. Treatment with adrenocorticotropic hormone up to 80 mg./day was carried out for 17 days. At the same time physiotherapy was started. As the adrenocorticotropic hormone was gradually discontinued, testosterone was instituted at doses of 50 mg./day and was continued for 9 mo. and 30 mg./day for 3 more months. During the administration of adrenocorticotropic hormone there was some slight increase in muscle strength. Coincident with the institution of the testosterone therapy there was a marked increase in appetite and a weight gain of 2.5 kg. in 2 wk.

Over the course of the next 5 mo. (apart from one brief period of exacerbation concomitant with a decrease in the testosterone dosage) there was steady improvement. The rash almost entirely disappeared and the child was very active, had good muscle strength and was able to roller-skate. After 1 yr. of testosterone therapy moderate enlargement of the clitoris and early growth of pubic hair were apparent. The mother described the patient as being a "tom-boy," but no abnormal increase in bone age was demonstrated. The remission has continued to the present time 3-6/12 yr. after the onset of the disease.

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NEWS AND ANNOUNCEMENTS

DEDICATION OF THE PHILIP CHARLES JEANS PEDIATRIC LIBRARY, STATE UNIVERSITY OF IOWA

The annual postgraduate conference in pediatrics was held at the State University of Iowa, Sept. 16 and 17, in conjunction with the fall meeting of the state Pediatric Society. One session was devoted to a memorial program honoring Dr. Jeans. Speakers at this session were Dr. Jean V. Cooke, Professor Emeritus, Department of Pediatrics, Washington University, St. Louis; Dr. L. A. Maynard, Professor and Head of the School of Nutrition, Cornell University, Ithaca, and Chairman of the Food and Nutrition Board of the National Research Council; Dr. James R. Wilson, Secretary of the Council on Foods and Nutrition, American Medical Association. Particular emphasis was given to Dr. Jeans' long service and many contributions as a member of national advisory boards, for this phase of his professional life was less familiar to physicians of the state.

The dedication followed the talks. Dr. Lee Forrest Hill of Des Moines read a eulogy of Dr. Jeans. The library was then dedicated to Dr. Jeans by Dr. Charles D. May, Professor and Head of Pediatrics, State University of Iowa. The dedicatory plaque reads as follows: "This library is dedicated in appreciation of Philip Charles Jeans, M.D., Professor and Head, Department of Pediatrics 1924-1952. A wise clinician, thorough investigator, humble teacher, and understanding friend."

BOOK REVIEWS

CONGENITAL DYSPLASIA OF THE HIP JOINT AND SEQUELAE, Vernon L. Hart, M.D., Springfield, Ill., Charles C Thomas, Publisher, 1952, $5.00, 187 pp.

This is a book of particular value and interest to pediatricians, although written by an orthopedic surgeon. It explains concisely and graphically the early signs of hip dysplasia, as well as the need for early diagnosis and treatment. The use of the Frejka abduction pillow splint is advised when diagnosis can be made in the preweight bearing period; this method of therapy is almost always successful and easy to apply, in contrast to the discomfort of plaster casts and less favorable results obtained in older infants and children. Approximately one-half of its 187 pages consist of photographs and x-ray reproductions illustrating the text.

The author completed the book before his untimely death in the summer of 1950. He first became interested in congenital dislocation of the hip in 1935 when he was able to trace osteoarthritis of the hip in an adult back to subluxation in infancy. Since then he has found numerous cases of a similar nature, leading him to believe that congenital hip dysplasia is much more common than previously realized. Dysplasia is defined as an interruption of normal maturation of the hip joint and femoral head, with a cartilaginous, pliable and deformable acetabulum. A large percentage of such hips undergo spontaneous recovery, others persist in subluxation, while others dislocate after weight bearing begins. Etiology is uncertain in most cases, genetic, biologic and mechanical factors playing a role.

Hart states that diagnosis is ordinarily not made until weight bearing has begun. He asserts that pediatricians in general are not aware of the early signs and implications of dysplasia of the hip.

CHILD PSYCHIATRIC TECHNIQUES, Lauretta Bender, B.S., M.A., M.D., Springfield, Ill., Charles C Thomas, Publisher, 1952, $8.50, 360 pp.

This book is a collection of original papers by Lauretta Bender, Paul Schilder and their coworkers, covering observations of children for over 15 years at Bellevue Hospital. It is a "diagnostic and therapeutic approach to normal and abnormal development through patterned, expressive and group behavior." The book opens with a brief historical survey of child psychiatry, outlining important schools of thought and the development of special technics and social institutions in the study and treatment of disturbed children.

The original papers fall into roughly 3 groups: 1. The principles of patterned behavior are interpreted from observations of children with behavior disorders. The concept of body image maturation and experience is an especially important and interesting insight into childhood behavior.

2. The use of color and form by children with behavior disorders is described, and the relationship of this to psychologic theories of esthetic expression is elaborated.

3. There are descriptions of various art form expressions as methods of individual and group psychotherapy. This section is introduced by a discussion of psychotherapy on a children's ward where group activities are emphasized.

This volume is the first of 3 planned by Dr. Bender to report from her long experience in child psychiatry. The next 2 volumes will utilize the same patient material from Bellevue Hospital to discuss psychopathology and clinical psychiatric syndromes of childhood. The author summarizes her attitudes toward emotional disorders in children by stating, "Behavior problems, psychopathic or neurotic reactions, and conduct disorders arise from deprivations in the satisfaction of the child's basic needs and drives due to a failure on the part of parents or parent substitutes, or the constitutional weakness or organic disease in the child."

Because of the intrinsic difficulties in assembling individually written papers into a book, it is frequently difficult to perceive continuity in this volume. However, the uniformity of scientific outlook, the consistent assumptions on which hypotheses are constructed, and the classically valuable descriptions of sick children and the course of their illness cancel out this disadvantage. Although one may not agree with certain of the assumptions, the basic principles of psychoanalysis, gestalt

psychology and neurology are here utilized for a provocative and rewarding description of deviant child behavior. Problems of retardation in personality development are emphasized.

It is safe to say that few have the amount of patient material with long follow-up contacts that the Bellevue group have. The value of this perspective with the richness of clinical description makes this an historically important book in child psychiatry.

Pediatricians may find this opus a highly specialized way of looking at children, especially when they find themselves enmeshed in attempted correlations of gestalt psychology, psychoanalytic concepts and the psychologic implications of abstract art in discussing the behavior and drawings of individual patients. For those interested in ". . . the projective, creative, configurational and group behavior" of children, this is a book that will answer many questions, pose many more, and stimulate further interest in the subject. It is a superb opportunity to read how a versatile group of medical workers have looked at, listened to, and thought about the behavior of disturbed, unhappy and retarded children for over 15 years. The chapters on creative dance, puppet shows, clay modeling, and sidewalk drawings and games are especially stimulating.

The statements referable to criteria for aesthetic expressions will be questioned by many as too neatly formulated and too psychopathologically oriented. However, as a source of fruitful hypotheses for work with children, these statements are helpful. There is an excellent bibliography and index.

CHILDHOOD EXPERIENCE AND PERSONAL DESTINY, William V. Silverberg, M.D., New York, Springer Publishing Co., 1952, $4.50, 289 pp.

Parents properly seek guidance from their pediatricians in child-rearing practices. In recent years pediatricians have been increasingly interested in the clarification they can expect from psychoanalysis about problems of child rearing. The most important contribution of the above book, written by a New York psychoanalyst, is the attempt to show how the reconstructive data gained from the psychoanalysis of adults can give insight into the effect of childhood experiences on personality development.

Dr. Silverberg's book is well organized, and he is to be congratulated for attempting to throw light on this difficult and important area. It is regrettable, however, that he does not distinguish sufficiently between speculative psychoanalytic hypotheses, that are so fruitful in looking backward, and the empirically workable practices that come from keen direct observation of children in the home, nursery school, doctor's office, hospital and playroom. Although the reconstructive data of psychoanalysis has been the richest source of constructs concerning personality development, direct observational data is essential before we can verify or invalidate many of the crucial hypotheses about what constitutes a healthy personality, what child-rearing practices can be advocated and how they can be imparted to parents in a helpful way.

The book is introduced by a chapter, "The Need for a Theory of Personality." The next 2 chapters offer such a theory, which is essentially the psychoanalytic theory formulated by Sigmund Freud, that has been added to and modified by later workers. The author pays special attention to the stimulating contributions of Harry Stack Sullivan. Chapters 3, 4 and 5 elaborate this theory in terms of the psychosexual and psychosocial development of the child. This is organized around the experiences and conflicts of orality, anality and discipline, and genitality and rivalry. There is a final chapter on "Psychotherapeutic Aims" and a helpful bibliography and index. The author has a flair for clear description that elucidates technical psychoanalytic terminology and concepts.

Although many psychoanalysts will differ in emphasis and interpretation of certain theoretic considerations, the author goes to the core of personality development when he describes the individual's ways of adapting at different levels of maturation to the thoughts, feelings and phantasies of inner experiences and to varying interpersonal experiences. Not enough attention is given to constitutional differences.

The pediatrician with an enormous fund of direct observational data from his everyday contact with child-rearing problems will find psychoanalytic insights stimulating and helpful in understanding a child's development. It would be an error, however, to use psychoanalytic hypotheses as facts or to substitute them for what the physician sees, hears and senses from his patients and their parents. With these considerations in mind this book can be recommended as worth while reading.

HEILPÄDAGOGIK, Hans Asperger, Vienna, Springer-Verlag, 1952, $4.30, 280 pp.

There is no English translation for the German word *Heilpädagogik*, yet we may define it as educational treatment of neuropsychopathologic disorders of children. The German school limits this activity field to mental retardation, whereas the Austrian concept comprises a far wider range. This is due to the fact that Vienna has played a leading traditional role in the research development of child psychopathology. Freud, Adler, Bühler and Economo had great influence not only on pediatric psychology, but on sociology and normal pedagogy. Pirquet was the first to connect the Vienna University Children's Hospital with a psychopathologic department. Forty years ago, Erwin Lazar was its first chief physician, and his work is continued by the author of this book. A volume like this, composed for mediual students, educators and sociologists, co-workers of such different background and training, is not only forced to compile in the glossary of medical terms such heterogenous subjects as granulation tissue and autism. Also in the text presentation, compromises are inevitable. Topics like psychology of character are too profound for the average pediatrician, and postencephalitic disorders are beyond the capacity of the educators. The author prudently plows the common ground of observations, avoiding theories and deductions from preconceived ideas.

Such an approach guarantees a practical basis for cooperation, though differentiation of modern clinical entities is sometimes sacrificed. The EEG is not mentioned, speech disorders are treated too briefly, the chapter on psychopathy does not elaborate the distinction from mental defects. The section on various normal and abnormal motivations of lying is highly instructive.

Interpretations of childhood psychopathology differ under various patterns of civilization. Yet thorough observations are informative for every reader, particularly since they reveal manifestations brought on by the trying conditions of the aftermath of the war.